- OWS secured communications support for all ACTIV study teams through contract; it has been awarded and Avon is the manager; everything that will be done for the studies comes through that contract
- Starting social listening; will go out and check and see social media to identify what people are looking for so that will help inform the campaign; ready to do print support and ads.
    - Still trying to figure out what is the best channel to reach potential patients and healthcare providers (two-pronged approach)
- Website is in English and Spanish; all outreach materials will be developed in both languages.
- Have not yet started on engagement with community organizations but hoping to begin working with NPHIC (National Public Health Information Coordinators); hoping to get a web page on there and some information on the state websites as well.

Site Identification Efforts Updates (Stacey Adam, FNIH)

- (b) (4)
    - Started with ACTIV-1 and ACTIV-2.
    - (b) (4) partners completed the initial search and is conducting additional refinements for ACTIV-1.
    - (b) (4) partners completed the initial search and identified approximately 1260 potential sites for further assessment.
    - If ACTIV-3 or ACTIV-4 is interested in working with the (b) (4) team, please let Stacey know.
- (b) (4)
    - Continuing to push forward; vast majority of those sites are interested in ACTIV-2 and ACTIV-4 with a particular emphasis on ACTIV-4b. Continuing to follow up with those sites; the only two that are still outstanding are Puerto Rico and Hawaii
- (b) (4) and Follow-up
    - Thank you to everyone who participated on the webinar held on 12/22 to provide an overview of ACTIV trials.
    - Received interest from 10 sites; 5 of which are interested in more than one ACTIV study.
    - There are about 4-5 interested sites that we are still waiting to hear back from, but Hana, Helen, and Stacey will follow up with them.
        - Even split of interest outpatient and inpatient studies.

Pan-NIH Lessons Learned on Pandemic Response (Kevin Bugin, OWS)

- Would like to capture lessons learned from across the life cycle of the process from identifying and prioritizing the agents to designing the studies and executing them.
- Will document specific examples and turn this into a document that will be useful for the future; this document will include:
    - Risks and mitigations
    - Mistakes and efficiencies

ACTIV, Cross-Trial Operations Meeting

Thursday, January 7th, 2021

- Objectives: 1. Use this document to prepare for the future (in the case of another pandemic) 2. Influence drug development and improve clinical trial infrastructure
- Lessons learned will cover strategic and ops topics across trials:
    - Research, scoping, and prioritization (focus of OWS)
    - Infrastructure and resourcing (focus of OWS)
    - Clinical Trial execution (light-touch to connect with study team "lessons learned' efforts)
- Next steps: In the coming weeks, the hope is to 1. ID experts, participate in interviews and review a structured fact-base for priority topics 2. ID key themes from a fact-base to develop playbook, publications, presentations, etc. for a varied audience
- David Wholley spoke with Francis Collins about this and Francis will be identifying someone to work with Kevin on this from NIH

Remdesivir Supply Planning (Kevin Bugin, OWS)

- A couple of studies are working ahead for the procurement of Remdesivir for the studies in 2021; do not foresee any studies running out of Remdesivir in the foreseeable future – this is just planning ahead.
- OWS is helping out in two ways – 1. Provide funding to purchase more Remdesivir 2. Go to the SNS (National Stockpile) to tap into the Remdesivir that's there; this may be faster and cheaper for the US government

**Quick follow up on the ACTIV Cross Trial Meeting that took place in December; thank you to everyone who gave Stacey their ICFs; the Deloitte team is working on cross-walks and creating a list for the validation of what biospecimen samples are being generated within the trials.

CHAT

None for this meeting

High-Level Meeting Summary

Representatives of all ACTIV trial teams convened to receive trial status updates and discuss approaches to biospecimen prioritization. Participants agreed to develop a cross-ACTIV prioritization process and to discuss (during its next meeting) the design of the governance structure for this process.

Action Items

• Create proposed structure for the Biospecimen Prioritization Committee	Stacey Adam/Deloitte team
• Request and review ICFs (from trial teams) and CTAs (from trial sponsors) to identify any contractual obstacles to future studies of biospecimens	Stacey Adam/Deloitte team
• Assemble a “leftover specimen list” of study-specific biospecimens that could be used in future studies	All ACTIV trial teams
• Compile information from the above efforts and distribute the proposal and other relevant pieces for trial teams to review before their January meeting	Stacey Adam/Deloitte team

Cross ACTIV Biospecimen Prioritization

ACTIV leadership has identified the need to formulate a policy governing long-term use of biospecimens collected within ACTIV trials. Dr. Cliff Lane explained that the completion of ACTIV-3’s first study has already prompted a request to use stored specimens for additional testing, and such additional tests will likely be of interest both to study teams and external researchers. ACTIV leadership has thus called for conversation about the proper oversight structure for prioritizing such tests. The first question is whether use of specimens should be governed at the study level or instead through an overarching cross-ACTIV effort (potentially supported by NIH), which may help maximize samples sizes and minimize duplication of effort.

Representatives of ACTIV-1, -2, -3, and -4 (including trial leads and OWS advisors) unanimously agreed that a uniform cross-ACTIV governance structure would best support scientific decision-making designed to achieve a comprehensive examination of COVID-19 (members of ACTIV-5 were not available for this portion of the meeting). All teams present agreed that the governance structure should include trial team members and should be transparent about its prioritization model. Trial teams offered more specific observations summarized below.

Advantages of the Cross-Trial Approach

Maximize Full-Spectrum COVID Data

The ACTIV-1 team noted that an overarching approach would best suit the full-spectrum design of ACTIV trials, which is assembling a unique collection of specimens that range from early-stage outpatients to the recovered post-hospitalized population and that thus represent an opportunity to build a sequenced understanding of the full course of infection. ACTIV-4 emphasized this opportunity, suggesting that all enrolled patients might be represented in an overarching registry that would allow tracking over time and potentially improve identification of biomarkers (e.g., for attributes of "long-haulers").

Enhance Sample Collection in Real Time

The ACTIV-2 team noted that the timing of the prioritization effort also creates the possibility of *enhancing* the data collected by ACTIV, not just setting guidelines for its use. Because sample collection is ongoing, biospecimen prioritization efforts undertaken over the next several months could shape *prospective* sample collection by trial teams. ACTIV-4C agreed and noted that its outpatient kits could enable remote collection of blood spots and genomic DNA; ACTIV-4B noted the availability of funding to collect biospecimens beyond the needs of its core trial.

Support Collaborative Decision-Making

The ACTIV-3 team suggested that a cross-ACTIV governance structure would improve scientific decision-making by fostering collaboration and potentially by bringing trial team members into collaboration with external researchers with different perspectives.

Limitations

Lack of Sufficient Samples

Some studies may have more samples to repurpose than others. ACTIV-2, for example, has collected more samples than its protocol objectives require and has already begun using samples for a sub-study of immunology and vaccine responses. However, ACTIV-3's sample-sharing agreements with companies halve its volume of plasma and serum specimens, making its supplies scarce. As a pragmatic trial, ACTIV-4A does not require participation in its biorepository and expects approximately one-third of its sites to choose to participate. The target sample collection described in protocols may also not always predict actual sample collection at sites, leading to potentially lower stocks of stored biospecimen than expected. Thus, a prioritization effort would need to begin by creating an inventory of what samples are actually available for testing.

Contractual Restrictions

Some studies' CTAs or ICFs may impose contractual restrictions on subsequent studies of biospecimens. Dr. Stacey Adam has begun to collect and review these documents in order to determine the existence and extent of any such restrictions.

Challenges of Study Design

Even when sufficient biospecimens are available, combining them with samples from other studies may mix data collected in different ways and thus pose challenges for study design. Dr. Jim Neaton suggested that the prioritization effort should take account of this difficulty.

Prioritization Committee

Based on the trial teams' support, Dr. Adam proposed forming a prioritization committee to include two representatives from each of the seven ACTIV trials and several additional members from the ACTIV TX-Clinical Working Group (potentially from the private sector). Dr. Sarah Read recommended also including representatives of each NIH trial sponsor (i.e., NIAID, NHLBI, and NCATS), which may be involved in funding future biospecimen studies; representatives of OWS might also participate if they may contribute such funding.

Next Steps
Trial teams agreed to move forward to develop a cross-ACTIV prioritization process. Trial team members will develop and submit to Dr. Adam an initial inventory of their "leftover" biospecimens that may be prioritized for future studies. Dr. Adam's team will draft a proposal for the committee structure and circulate it in advance of the January Cross-Trial meeting. Questions for discussion include whether the committee will develop a list of prioritized topics to guide individual trial teams' biospecimen decisions or will instead directly adjudicate biospecimen-related requests.

Trial Status Updates

ACTIV-1

ACTIV-1 has opened 19 sites and (b) (4). The ACTIV-1 team is still identifying a small number of additional sites but is primarily focused on site activation, which has been slowed by the contracting process. A protocol amendment to resolve some issues with ACTIV-1 patient enrollment was approved on December 17.

ACTIV-2

ACTIV-2 has activated one site for Version 2 of its protocol, which will test Brii Bio's Ab cocktail. As each site begins testing the Brii agent, it will also cease testing (b) (4) antibody (Ab), with a deadline to stop all testing by January 15. Enrollment has increased dramatically during testing of the (b) (4) agent and the ACTIV-2 team will be assessing enrollment as it transitions from an EUA drug to a placebo-controlled trial. Version 3 of the protocol (which will add (b) (4)'s agent in IM and IV formulations, Synairgen's inhaled IFN beta, and oral camostat) has been presented internally to NIAID and is currently being reviewed by the FDA. Version 4 (which will test SAB's polyclonal Ab) was also presented at NIAID and will soon be submitted to CDER.

The ACTIV-2 team has begun considering how its collection of patient outcomes data can facilitate studies of long COVID and suggested that standardizing across trials could be useful.

ACTIV-3

ACTIV-3 has launched Version 2 of its protocol with 2 patients randomized at one of 6 open sites and an additional 23 sites activated. Version 3 has been submitted to the FDA and central IRB, and feedback is anticipated on December 19. ACTIV-3 continues to discuss with (b) (4) the possibility of onboarding its agent and is also organizing a trial testing (b) (4) (and potentially assessing futility of remdesivir) in high-flow and mechanically ventilated patients. ACTIV-3's publication on its first trial will be released during the week of December 21.

ACTIV-4

ACTIV-4A has activated 22 sites in the U.S. and 2 in Spain and has (b) (4); including its multi-platform collaboration with ITAC, REMAP-CAP, and PROTECT trials, it has over 3,000 patients. DSMBs from ACTIV-4, ITAC, and REMAP-CAP are currently reviewing study data submitted in November. In response to comments from the CONNECTS Steering and Executive Committees and from NHLBI, ACTIV-4A has revised a plan to add a third arm testing a P2Y12 inhibitor plus prophylactic-dose heparin; if *full*-dose heparin generates adequate safety data, another arm will launch to test that dose in combination with the P2Y12 inhibitor in a subset of qualifying patients. ACTIV-4A continues to consider a variety of new agents. It is working to collect information to understand long COVID, including information about patients' pre-COVID health.

ACTIV-4B has opened 3 sites that have (b)(4). The trial has opened 4 additional sites in Florida and Chicago and has completed contracting agreements that should add 20 to 40 sites by mid-January and 80 to 150 by the end of January. In collaboration with CVS and Coram Health, ACTIV-4B has designed a second low-touch pathway that will connect investigators to individuals who have tested positive for COVID-19 at CVS, enabling sample collection and trial randomization within 48 hours This effort has required approval from Bristol-Meyers Squibb and Pfizer (makers of the agents being tested in ACTIV-4B) and is expected to launch by the third week of January. ACTIV-4B thanked members of other teams for helping to arrange access to the Quidel antigen test, which has been very useful at sites.

ACTIV-4C has received final approval of its protocol from (b)(4) and approval from the FDA is expected early during the week of December 21. Drug is available for shipment as soon as approvals are received. The trial team is working on contracting with a set of network sites managed by the University of Pittsburgh and non-network sites to be managed by Covance (an additional 15 sites will open in Canada). When ACTIV-4C launches, which is expected by the beginning of 2021, it will enroll eligible ACTIV-4A patients at the time of hospital discharge; the trial team has established an EQ-5D survey to test people at discharge baseline and at post-90 days and is working with NIH to ensure protocol language supports this long-term follow-up.

ACTIV-5

ACTIV-5 has activated 7 sites and (b)(4). The trial team plans to activate at least one more site in the coming week. The trial team has encountered some challenges in securing approvals from local IRBs. OWS staff have expressed a willingness to assist if necessary.

Appendix A: Participants List

TRIAL TEAM MEMBERS

ACTIV-1

William G. Powderly, MD, *ACTIV-1 Chair and J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Sam Bozzette, MD, PhD, (not in attendance) *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Lisa LaVange, PhD, (not in attendance) *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Michael Proschan, PhD, (not in attendance) *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

ACTIV-2

David (Davey) Smith, MD, *ACTIV-2 Chair Professor of Medicine, U. California, San Diego*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Michael Hughes, PhD, (not in attendance) *Professor, Department of Biostatistics, Harvard University*

Cyrus Javan, MD, MPH, *Medical Officer/Program Officer, Division of AIDS, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

ACTIV-3

James D. Neaton, PhD, *ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen*

Birgit Grund, PhD, *Associate Professor of Statistics, University of Minnesota*

ACTIV-4

Judith S. Hochman, MD, *ACTIV-4A Chair and Harold Snyder Family Professor of Cardiology, Department of Medicine, NYU Grossman School of Medicine*

Paul Ridker, MD, *ACTIV-4B Chair; Senior Physician, Brigham and Women's Hospital; Eugene Braunwald Professor of Medicine, Harvard Medical School*

Tom Ortel, MD, PhD, *ACTIV-4C Chair and Chief, Division of Hematology, Department of Medicine, Duke University*

Scott Berry, PhD, *Adjunct Professor, Department of Biostatistics & Data Science, Kansas University Medical Center*

Jean Connors, MD, (not in attendance) *Associate Professor, Department of Medicine Brigham and Women's Hospital*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI, NIH*

Eric Leifer, PhD, *Mathematical Statistician, NHLBI, NIH*

Allison Morris, MD, *ACTIV-4D Co-Chair and Professor of Medicine, Immunology, and Clinical and Translational Research, University of Pittsburgh*

Frank C. Sciurba, MD, *Professor, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh*

Abdus Wahed, PhD, (not in attendance) *Professor, Department of Biostatistics, University of Pittsburgh*

Clinton B. Wright, MD, *Director, Division of Clinical Research, National Institute of Neurological Diseases and Stroke (NINDS), NIH*

ACTIV-5

John Beigel, PhD, (not in attendance) *Division of Microbiology and Infectious Diseases, NIAID, NIH*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases*

OPERATION WARP SPEED

Tom Stock, DO, *Clinical Advisor to ACTIV-1 and Former Vice President, Clinical Development and Operations, Pfizer*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, (not in attendance) *Clinical Advisor to ACTIV-3 and Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

David Douglas, *Clinical Advisor to ACTIV-4 and Former Head, Global Research and Development Project Management Office, Pfizer*

Ciaran Lawlor, PhD, (not in attendance) *OWS Consultant, Boston Consulting Group*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Sheri Parker, PMP, PhD, *CAPT, MSC, USN, Therapeutics Clinical Operations Director, Operation Warp Speed*

Ritika Philip, (not in attendance) *OWS Consultant, Boston Consulting Group*

Col. Deydre Teyhen, *DPT, PhD,* (not in attendance) *Director of Therapeutics, Operation Warp Speed*

TX-CLINICAL WORKING GROUP

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-Chair)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

OTHER INVITED ATTENDEES

Cynthia Boucher,
Kevin Bugin, PhD, (not in attendance) *Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)*
Krishna Deepak, MS, *Consultant, Boston Consulting Group*
Nancy Geller, PhD, (not in attendance) *Director, NHLBI Office of Biostatistics Research, NIH*
H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*
Raahul Ramakrishnan, MD, (not in attendance) *Project Leader, Boston Consulting Group*
Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems*
Austin Van Grack, MS, (not in attendance) *Committee Coordinator, Social and Scientific Systems*

STAFF

Evan Appell, *Consultant, Deloitte*
Alex Sorosa, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Bill Erhardt to Everyone: 08:49 AM

Does NIH have a policy with respect to subject consent for use of banked biospecimens? Particularly for investigations not envisioned in the original protocol?

From Libby Higgs to Everyone: 08:57 AM

Bill, there is usually a line in the consent allowing use of specimens for future scientific research. I do not think there is a blanket policy. Others on the NIH side please correct me if I am wrong.

From Currier, Judith, M.D. to Everyone: 09:00 AM

We have a consent for use of stored samples in ACTIV_2 Happy to share

ACTIV, Cross-Trial Operations Meeting

Thursday, December 17th, 2020

Action Items

Action Items		
	Information	**Owner(s)**
1.	Follow up with Chris on the progress of the HHS Portal and Call Center in January.	**Stacey Adam**

Meeting Summary

- ACTIV-3 Preliminary report on Lilly agent accepted in NEJM and due to be published on December 22.
- Convalescent Plasma trials are doing well and picking up speed.
- Portal and call center experiencing significant traffic; advertising to begin shortly.
- PICS Contract is on track with timeline and negotiations should commence soon.

Notes

Agenda

- Opening and Welcome
- ACTIV Trial Status Update
- HHS Portal and Call Center Update
- Community Provider Engagement
- PICS Contract Update
- Meeting Recap

ACTIV and Convalescent Plasma Trials Status Update

- ACTIV-1: 19 sites open; (b) (4) led as of 12/17
  - Submitted amendment 1 to IRB on December 3 and FDA on December 4
    - Will be hearing back today (12/17)
  - Evaluating and selecting participating sites
- ACTIV-2: 80 sites open; (b) (4) as of 12/16
  - 222 in Phase II – 700 mg; 153 in Phase III – 700 mg
  - Received "Safe to Proceed" from the FDA on V2 of the protocol on December 3
  - (b) (4) (as of 12/16) and onboarding new agents
  - Preparing to send V3 of the protocol to the FDA (early next week); V4 going to the FDA in the next couple of weeks

**COVID likely to become an endemic disease; there is an opportunity now to study this disease before the vaccine becomes more widely available; hoping individuals will volunteer altruistically, for the good of humanity, as opposed to thinking there is some benefit to them

- ACTIV-3:
  - Received IRB and FDA approval on V2 of the protocols; this allowed for the opening of (b) (4) first patient in last night

  - Finalizing V3 of the protocol; will include (b) (4) has been a bit slower getting through DSMB Review
  - Preliminary report on (b) (4) data in NEJM due to be published on next Tuesday, December 22
  - Version 3 should be approved this week from the IRB and the FDA; there will be an ACTIV-3b which will be another appendix to the trial (b) (4)
  - 13 sites already registered for OM4
- ACTIV-4:
  - Hospitalized: 36 sites; 398 patients as of 12/16
  - Pre-hospitalized: 7 sites; 49 patients as of 12/14 (strategies using CVS as satellite sites for the trials; this contract should be up and running by mid-January)
  - Post-hospitalized received "safe to proceed" from FDA
    - Launch date: Next Tuesday (12/22); anticipating a mid-January timeframe to enroll first patient
- ACTIV-5 (Big Effect Trial): 5 sites open; (b) (4) as of 12/14
  - Screened close to 450 sites, of those they found about 40 that they think are viable, and of those they have only had about 15 fill out the paperwork
  - Prioritizing additional investigational sites; not pulling from other ongoing trials so this is posing a bit of a challenge
- Convalescent Plasma Trials – doing well and picking up speed
  - CONTAIN COVID-19
    - 16 sites; 611 patients as of 12/16
    - DSMB meeting 12/4 – reviewed data from first 430 patients
    - Adding up to 14 more sites
  - PassItONII
    - 18 sites; 383 patients as of 12/16
    - DSMB meeting on 12/9 – reviewed data from first 150 patients
    - Adding up to 15 more sites
    - A data consortium called (b) (4) as well as other convalescent plasma RCTS and they will be meeting tomorrow and issuing recommendations. These recommendations usually take till about Wednesday of the next week, so we expect them before Christmas, but maybe in January (due to the holidays).
  - C3PO
    - 49 sites; 328 patients as of 12/7
    - Adding up to 19 more sites
    - The first DSM will look at the sample size re-estimation; the original is 600 subjects – they will decide whether they need to increase or decrease this number.
- OWS/NCATS planning **Plasma Assay Summit** in early 2021. The focus will be on the harmonization of the assessment of plasma potency in convalescent plasma clinical trials so that trial results can be compared and plasma potency directly linked to clinical outcome. The USG stakeholder call was held on 12/14.

HHS Portal and Call Center Update (Chris Shreeve, OWS)

- In the first week → 30,000 visitors (very robust considering no advertising yet).
- Most people are coming in on government websites; Links on other government sites are a major source of traffic (especially link from CDC.gov – this is a tops source of traffic)
- There may be trouble getting through the noise of the vaccine; people do not usually search for clinical trials.
    - A contractor will come on board on 12/24 to help with advertising for individuals to still come on board these trials despite the release of vaccines.
- Promotional efforts:
    - Dr. Woodcock is speaking at an AARP tele townhall (Thursdays at 1:00; audiences of up to 50,000 across the country); speaking about what you need to know about treatments and vaccines (Q&A format) – watch on demand here.
- In the middle of doing a slight redesign to the portal to make the action in the front a bit stronger – "We need you to participate" message.
- Questions:
    - Crystal: How did you manage to get links to the CDC website and to other (local/statewide) government sites?
        - Reached out several times, but this has not happened yet.
    - Stacey: Have there been social media packets (for Facebook, Linkedin, etc.)
        - Graphics and tweets are ready and they have been sent out; NIH is handling this piece of it.
        - Not all have been IRB approved; the portal and call center have had to pull theirs back because they were not IRB approved yet.

Tech Enabled Site Management Organizations (SMOs)

- Many trials have identified the need to tap into community providers, but one of the challenges about community sites is that they are not set up to run clinical trials. One possible solution that you can work with a Tech-Enabled SMO to plug those community sites into an existing larger site that is already set up and part of a trial; this is referred to as a hub and spoke model.
- ACTIV-2 and ACTIV-4 have been exploring this model; still early for ACTIV-2 (currently more conceptual than reality, but ready to try a few pilot studies → 3 month implementation period)
- Key Activities: site sourcing, site management, patient referrals, and data management

PICS Contract Update (Kevin Bugin, FDA/OWS)

- On track with timeline; begun initial technical review (deadline of December 14) and negotiations should begin right away
- Encouraging submissions

ACTIV, Cross-Trial Operations Meeting

Thursday, December 17th, 2020

CHAT

- **Sarah Dunsmore**13:40

Not just you Stacey

- **lmcnay**20:27

13 sites registered for 014

- **Libby Higgs**28:49

The ACTIV affiliated (b) (4) study has (b) (4).

- **Stacey Adam**29:13

Thanks, Libby!

- **chris shreeve**36:30

Dr. Woodcock AARP Town Hall today

- **chris shreeve**37:31

Program is offered to the public via five different channelso (855) 274-9507 (Dial in)o https://www.facebook.com/AARPPrograms (Facebook Live)o www.aarp.org/coronavirus (AARP Web site)o https://vekeo.com/aarp (Vekeo)Program is offered to the public via five different channelso (855) 274-9507 (Dial in)o https://www.facebook.com/AARPPrograms (Facebook Live)o www.aarp.org/coronavirus (AARP Web site)o https://vekeo.com/aarp (Vekeo)

ACTIV, Cross-Trial Operations Meeting

Thursday, November 19th, 2020

Action Items

Action Items		
	Information	**Owner(s)**
1.	Send CEAL slides and the zip file to Stacey Adam.	**George Mensah**
2.	Send short email to the CEAL team describing the communication strategy and what CEAL can do to help	**Chris Shreeve**
3.	All trial teams to send most recent consent version and any DSAs from all trials to Stacey Adam	**ACTIV Trial Teams**
4.	Collect list of sites from each of the ACTIV trial teams.	**Stacey Adam**

Meeting Summary

- Dr. George Mensah: Update from CEAL Team on enhancing minority and underserved population recruitment.
- Round robin status updates
- Trial data sharing: follow up.
- Update on site identification efforts.

Notes

CEAL Team: Enrollment/Recruitment/Outreach

- George Mensah: CEAL Team
    - CEAL is an NIH wide effort to increase diverse participation in trials in response to the recognition of the disproportionate impact of COVID on racial and ethnic minorities. CEAL has two core objectives: 1. Support the conduct of urgent community engaged research and 2. Outreach to address misinformation and mistrust within racial and ethnic minority communities.
    - Two program support members: Dr. George Mensah and Monica Web Hooper.
    - As studies are being rolled out, the CEAL team can perform a cross match and will be able to inform their teams of study sites to aid in the enrollment and recruitment so as to increase participation in studies.
    - CEAL can provide a comprehensive set of engagement and communication tool kit that is public and modifiable.
- Jane Atkinson: Who should we talk to in order to obtain CEAL materials and modify them with the ACTIV-1 information? Stacey Adam
- Based on funding, CEAL may expand beyond the 11 states where they currently have teams operating.
- Chris Shreeve: Provided a quick snapshot of the Combat COVID portal – Combatcovid.hhs.gov (so the CEAL team is aware of what will be coming)
    - Chris has been doing some of the communications around OWS; they are working to create a larger communication strategy for the studies to help them locally. They would like to coordinate with CEAL for minority outreach in the study sites.

ACTIV, Cross-Trial Operations Meeting

Thursday, November 19th, 2020

ACTIV Trials Status Updates

- ACTIV-1: 14 sites open; (b)(4) as of November 18, 2020.
  - Primary focus is getting sites up and running and getting those sites accruing patients.
- ACTIV-2: 68 sites open; (b)(4) of those on the 700 mg dose as of November 18, 2020.
  - Completed enrollment for phase two for the (b)(4) agent and will be closing the randomized placebo-controlled portion of that. Will be converting to an open label study on the (b)(4) product, based on the EUA granted last week.
  - Keep the study running through open-label until (b)(4) antibodies are up and running, then the (b)(4) arm will close and convert back into being a placebo-controlled trial.
  - Multiple agents are looking to come into the ACTIV-2 trial.
- ACTIV-3: 51-60 sites eligible; not open yet because there is no drug at the sites or approved protocol
  - Second version of the protocol was submitted to the FDA on November 4; now awaiting final sign-off from the FDA by the end of the week of November 23 and reopening of sites the following week
  - 326 patients were accrued to the (b)(4) agent when the interim analysis was performed.
  - Beginning to explore agents that are not just neutralizing antibodies
- ACTIV-4: hospitalized → 14 sites open; (b)(4) as of November 18. Pre-hospitalized → 4 sites open; (b)(4) - additional sites in the works
  - NHLBI continuing to review agents and a third agent may come in to the hospitalized cohort
  - Post-hospitalized cohort is still on target to launch by the end of November
- ACTIV-5: 2 sites open; (b)(4)
  - Continuing to evaluate additional agents and pushing to get more sites open
- Sarah Dunsmore: Convalescent Plasma Trials update
  - Contain COVID-19 (run out of NYU in NYC) is up to 468 patients and 16 sites
    - Continuing to add sites; goal is to get up to around 30 sites because the target enrollment is 1000 patients
    - DSMB meeting on December 4
  - Pass it On II (run out of Vanderbilt) hit 200 patient mark (closing in on 25% enrollment) and 14 sites
    - 1000 patient target enrollment
    - Adding one to two sites a week – close to 30-35 sites
    - Major barriers to enrollment operations are competing trials, staff bandwidth, and blood products (there is a lot of resistance, particularly in underrepresented populations and receiving blood products)
  - Both trials can benefit greatly from communication materials (presented by Chris earlier)
- Lynn Marks: CPPO Convalescent plasma outpatient study – (b)(4); 31 sites → target number is 600 subjects

ACTIV, Cross-Trial Operations Meeting

Thursday, November 19th, 2020

ACTIV Trial Data Sharing

- Attempting to find a way forward; some discussions to share it externally to merge with some of the company data that it's being shared through the (b) (4)
- Possibly a way to share all of the NIH trials on a database platform that the NIAID team is building; Michelle Culp has been working on that with the technical team
- Need most recent consent version as well as any DSAs from all of the trial teams; Stacey and Michelle will review and determine if amendments are needed
- Next step: discussions on whether or not each CTA is allowed for data sharing

Site Identification Efforts Updates

- Kevin Bugin reached out to 13 large IDNs; only heard back from two, but there is a follow-up plan with these two IDNs
- David Wholley and Stacey Adam had a conversation with (b) (4) to bring them into ACTIV-2, but would also like to expand beyond that; they shared ACTIV-1-5 protocols with them and now their internal research team is doing evaluations of those protocols
  - (b) (4) would like Stacey to set up a couple of webinars for the sites to ask questions: separate webinar for outpatient and inpatient would be best
  - One or two representatives from each ACTIV team will be asked to join those webinars and do a short overview as well as address any questions that they might have
- Conversation with (b) (4) ; they are very excited about doing outpatient trials
- (b) (4) conversation to occur on Tuesday, November 24.
- Site requirement write-ups ad trial explanations were sent to the Society for Clinical Research and they will be posting this for all of their sites. They may also help with patient recruitment.
- Master site list of all the trials would be a good idea to keep tabs of existing and perspective sites for all trials. Stacey will be reaching out to ACTIV teams for list of sites as well as establishing a regular cadence to update this list.

Chatbox

06:58 George Mensah:

Christine, this is George Mensah. Can you hear me?

08:05 Christine Illanes:

Yes

08:14 Christine Illanes:

Sorry for the delay, I had my audio set wrong

08:33 deydre.teyhen:

We can hear you.

08:34 Christine Illanes:

Yes, I can hear you

09:44 George Mensah:

Thanks!

ACTIV, Cross-Trial Operations Meeting

Thursday, December 3rd, 2020

Action Items

	Action Items	
	Information	**Owner(s)**
1.	Review trial-specific content on the HHS portal and let Chris Shreeve know if any changes are needed	**ACTIV Trial Leads**
2.	Check with HHS on the requirement / process for IRB review of the website content	**Chris Shreeve**
3.	Share ICF with Stacey Adam and denote the following: 1) whether the trial team would have leftover samples; 2) whether the trial team is willing to contribute to the central repository; 3) any issues and/or barriers	**ACTIV Trial Leads**
4.	Follow up with CONNECTS colleagues to understand the status of their central repository effort	**Stacey Adam**

Meeting Summary

- Convalescent Plasma trials are experiencing shortages in high-titer plasma, especially in rare blood types
- Partnering companies (b) (4)) have been working with ACTIV-1 and ACTIV-2 teams to mine the (b) (4) to identify additional sites for the studies
- Promotion for the HHS Portal is underway. Team will confirm whether content on the website needs to be put through IRB for each study
- Team reviewed the scope and timeline for the Communication Contract
- Team agreed that the current ad hoc trial placement process works well and does not need to formalized

Notes

ACTIV Trial Status Update [Refer to Presentation]

- ACTIV-4
  - Pre-hospitalized cohort: 5 sites open; (b) (4)
  - Post-hospitalized trial is poised to be launched pending resolution of shipment issues
- ACTIV-5: 5 sites open; (b) (4) ; opening more sites this week
- Convalescent Plasma Trials Update
  - Contain COVID-19: 16 sites open; (b) (4) ; DSMB meeting this Friday (50% enrollment milestone)
  - PassItOn II: 14 sites open; (b) (4)
  - Challenges / Issues
    - Seen an uptick in enrollment but many hospitals are running at full capacity; team is brining on more sites
    - Challenge with staff fatigue – limited bandwidth to screen for trials
    - Shortages in high-titer plasma, particularly in rare blood types
      - Websites and continued PR efforts would help with plasma donations

        - Also working with blood banks to provide up-to-date science and guidance to encourage donation closer to recovery time
        - Lynn Marks: Team is working through the Rosetta project to understand what high-quality plasma means (i.e., not just about binding affinity but also neutralizing activity)

TransCelerate Investigator Registry Mining

- [Refer to Presentation for Background and Progress]
- Intend to leverage this partnership with other ACTIV trials
- Jane Atkinson: Team has been spending a lot of time to identify new sites – has been calling individual sites but hospital staff has been occupied. This partnership is really helpful.
- Stacey Adam: (b) (4) is excited to join ACTIV-1 but there are some contractual issues

HHS Portal Launch Update

- Promotion for the HHS Portal will com from Francis Collin's Communication office
    - No press release; via email to stakeholders, media, congress, etc.
    - Also running a paid search with HHS
    - Francis mentioned the website during a primetime interview with CNN
- Bill Erhardt: ACTIV-2 is also running a paid search – how do we coordinate and not compete with each other? Ideally these initiatives should be synergistic
    - Chris Shreeve: Would need to look at the search terms between ACTIV-2 and HHS. Once the communication contract is rewarded, there will be a third-party vendor who will also put forward a large paid search program
- John Beigel: On the website, contents related to patient recruitment and site recruitment are mixed – "I'm a Doctor" directs to the same site as patients and family members. Any way to break that down instead of having the same message?
    - Chris Shreeve: Team knew it would be an issue but didn't have the time or resources to differentiate. For ACTIV-5 it was addressed via the call center
- John Beigel: Has the website content been cleared by the IRB, as they are subject to patient recruitment?
    - Chris Shreeve: The call center script and FAQ have been approved by the IRB but not the website content
    - Stacey Adam: ACTIV-2 website content has been put through the IRB. Language on the HHS Portal was pulled from the NIH ACTIV website that have been approved by the IRB, but the content has not been recently re-vetted
    - IRB for each study would need to approve

PIC Communication Contract Update

- [Refer to Presentation for Scope and Timeline]
- Provider-targeting materials would be robust, detailed, and comprehensive

- Patient-target materials are more succinct, intended to drive them to the CombatCOVID website
- With Media campaign, would like to create an "identity" for each of the trials, both at the national level (championed by Drs. Francis Collins and Janet Woodcock), as well as at local level, i.e., championed by each trial teams
- Would develop content for all trials but would also need to assess trial-specific requirements / needs – team will reach out to have one-on-one meetings with each trial around late December / early January

Process for Trial Placement

- [Refer to Presentation]
- John Beigel: Part of the assessment is around bandwidth for the platform and where we are at - with the agent prioritization team wouldn't have insight for those considerations. The process works as many intangible things need to be considered
- Libby Higgs: For ACTIV-3, the inpatient study at the moment only includes mAbs which leaves a gap for high-flow patients. (b) (4) is an excellent fit to address the gap at this moment in time. The trial team is also considering a 2x2 factorial design with (b) (4)
- Jane Atkinson: Not sure how to make it a more formal process. Would be a case-by-case consideration with specific agents
- Rachel Harrigan: Trial resources and capacity at the moment need to be factored in. Not sure how to formalize into a standardized process
- Hilary Marston: NIAID is not at a position to take in more agents
- Team agrees that the current ad hoc cross-trial adjudication process works

Process for Trial Placement

- [Refer to Presentation for Context]
- David Wholley: This is not intended to be a physical repository, more a secondary review process to field various sample requests
- Jane Atkinson: ACTIV-1 does not have the funding for long-term storage – it has been a central question around whether there will be residual samples
    - David Wholley: This is precisely the type of feed back we are looking from the trial teams – we want to understand the issues and barriers and surface them to the leadership
- John Beigel: No apprehension this the idea of establishing a central repository. We went to ACTG who had a process already established – imagine other large organizations already have this infrastructure set up that this group can look into
- Rachel Harrigan: CONNECTS is setting up a central repository for NHLBI studies – it would be good to understand the state of that effort

Chatbox

Hilary Marston 27:52

are you considering buying some of the similar URLs for redirect? combatcovid.com etc

Thursday, December 3rd, 2020

chris shreeve 40:09

I will check with HHS -- they are managing the site. Thanks

High-Level Meeting Summary

Representatives of all ACTIV trial teams convened to receive trial status updates, review the proposed plan for a Biospecimen Prioritization Committee, and discuss emerging clinical trial results and their implications for standard of care and trial design. Trial leaders continue to await guidance from the NIH COVID-19 Treatment Guidelines Committee before modifying their control arms, but trials with SOC control arms have struggled with sites moving faster than that Committee. ACTIV-4A has generated interim results suggesting that therapeutic anticoagulants are effective for moderately but not severely ill hospitalized patients.

Action Items

• Review the crosswalks of specimens and ICFs with a focus on identifying missing, misconstrued, or unbanked specimens	Trial Team members

Trial Status Updates

ACTIV-1

ACTIV-1 has (b)(4) patients at 34 sites, with the pace of site opening accelerating. The trial has received safe-to-proceed approval from its DMSB and expects the next DSMB review in late March or early April. The team is addressing challenges in the (b)(4) trial arm, due to ICU physicians' reluctance to use an oral agent in patients on or about to begin ventilation.

ACTIV-2

ACTIV-2 has activated 99 sites for Version 2 of its protocol and has (b)(4) at 41 sites to the (b)(4) cocktail arm. The team anticipates reaching FPI on Version 3 and submitting Version 4 of its protocol to FDA on January 29.

ACTIV-3

ACTIV-3 is conducting Version 2 of its protocol with (b)(4) at 38 sites to agents from (b)(4). The ACTIV-3 team received safe-to-proceed approval from its DSMB on January 25. The team expects (b)(4) agent shortly and is in active discussions to onboard (b)(4)' agent. Data thus far suggest that the agents from (b)(4) do not lose efficacy against emerging viral variants. ACTIV-3B, a protocol for sicker patients on (b)(4), is under review by FDA.

ACTIV-4

The ACTIV-4A update is included in the summary of Dr. Judy Hochman's presentation (page 5).

ACTIV-4B has (b)(4) at 8 active sites. The trial's DSMB review has been scheduled for March. The ACTIV-4B team is working to add sites and is preparing a touchless remote model that will allow additional enrollment.

ACTIV-4C has shipped drug to its first site and expects FPI on Monday, February 1. The ACTIV-4C team has two additional Vanguard sites that are expected to open shortly and an additional 32 non-network sites have passed pre-assessment. Covance is finalizing its contracts so that it can open these non-network sites.

ACTIV-5

ACTIV-5 has opened 11 sites and (b)(4). An additional 20 sites are in the process of IRB contracting. The trial team is exploring options for BET-C and -D, with a focus on accounting for evolving standards of care.

Convalescent Plasma Trials

Contain COVID-19 has (b)(4) at 19 sites and PassItOnII has (b)(4) at 22 sites, with the potential for 11 more. Both inpatient trials have held regular DSMB review meetings, with interim analysis of PassItOnII slated for mid-March. The outpatient C3PO trial has (b)(4) at 51 sites. The C3PO team plans a meta-analysis with other convalescent plasma trials.

ACTIV Biospecimen Prioritization Committee

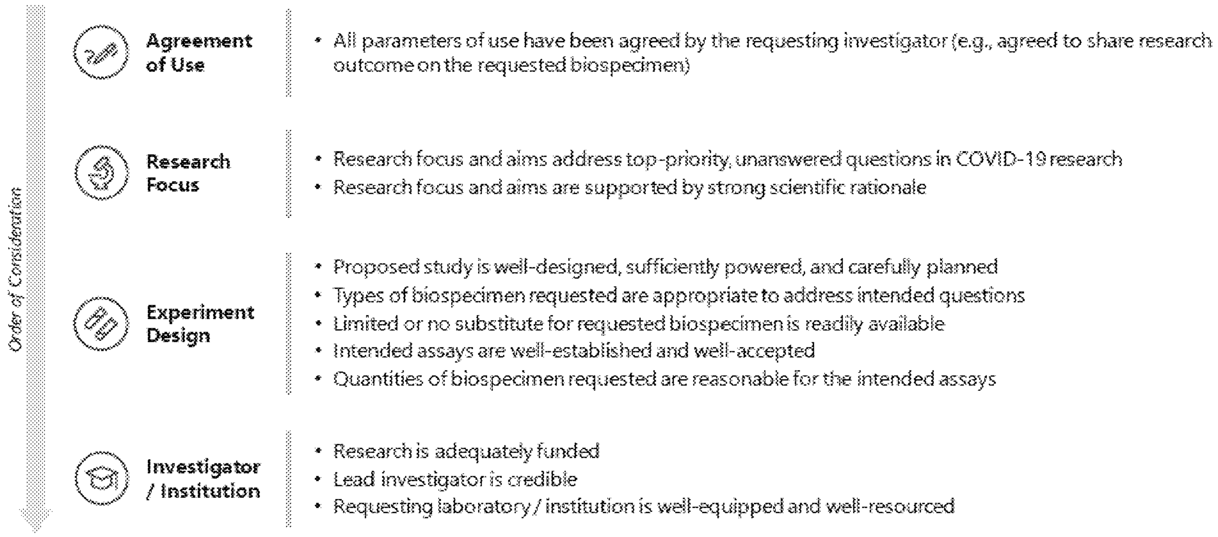
During the Cross-Trial team's December 2020 meeting, representatives of ACTIV-1, -2, -3, and -4 (including trial leads and OWS advisors) unanimously agreed to establish a uniform cross-ACTIV governance structure to oversee long-term use of biospecimens collected within ACTIV trials. ACTIV has developed a draft proposal for an ACTIV Biospecimen Prioritization Committee (ABPC), which would be charged with evaluating, prioritizing, and approving secondary research requests for biospecimens from across ACTIV trials, with the goals of accelerating scientific impact, maximizing clinical impact, and addressing the most significant scientific questions.

Scope

The ABPC will be responsible for all scientific aspects of biospecimen requests *outside of protocol-defined assays*. Scientific aspects include defining and revising scientific and clinical evaluation guidelines (including minimum requirements and prioritization criteria); collecting, evaluating, prioritizing, and approving/rejecting requests; and communicating review decisions. The Committee will not be responsible for non-scientific considerations: any samples identified as eligible for prioritization by this Committee will be prescreened for legal or other logistical hurdles (e.g., related to ICFs or CTAs). The ABPC is devoted only to prioritization; it is not functioning as a biobank and thus will not be responsible for management or facilitation of biospecimen collection, processing, storage, retrieval, and dissemination.

Proposed Guidelines

Dr. Stacey Adam presented a slide describing proposed guidelines for the ABPC's assessments (Figure 1). The foundational Agreement of Use would include a requirement that investigators make all research findings public. Drs. Jens Lundgren and Sarah Read suggested that the Research Focus category should include a requirement that assessments of biological material serve the common good and not only advance commercial goals.



Agreement of Use

- All parameters of use have been agreed by the requesting investigator (e.g., agreed to share research outcome on the requested biospecimen)

Research Focus

- Research focus and aims address top-priority, unanswered questions in COVID-19 research
- Research focus and aims are supported by strong scientific rationale

Experiment Design

- Proposed study is well-designed, sufficiently powered, and carefully planned
- Types of biospecimen requested are appropriate to address intended questions
- Limited or no substitute for requested biospecimen is readily available
- Intended assays are well-established and well-accepted
- Quantities of biospecimen requested are reasonable for the intended assays

Investigator / Institution

- Research is adequately funded
- Lead investigator is credible
- Requesting laboratory / institution is well-equipped and well-resourced

Figure 1

Structure

The proposed structure for the ABPC includes an Oversight Committee made up of one representative from each trial sponsor; a Review Committee made up of ACTIV trial team representatives, academic experts, and industry representatives (industry representatives are likely to be Therapeutics-Clinical WG members, who have been involved in ACTIV from its launch; and a Project Management team (initially composed of FNIH and Deloitte staff during the process to establish evaluation criteria and then provided by NIH as the ABPC begins to conduct its work). After this structure is approved by ACTIV leadership, trial teams will be contacted to identify specific individuals who should be involved.

Process

Investigators will submit proposals through an online form or portal. Reviews would occur on a biweekly basis, with the Project Management Team collating and distributing materials, the Review Committee completing assessments individually, and a group adjudication taking place as needed to resolve discrepancies. Based on the Review Committee's recommendation, the Oversight Committee would render a final approval or denial, which would be communicated to applicants by the Project Management Team. The public announcement of the submission process will be carefully timed to balance the desire for lead time to begin adjudication and the need to complete studies and unblind data before material can be released.

Open Questions for the Cross-Trial Team and ABPC

An inventory of trial samples must be completed for the ABPC's work to take place. Deloitte has assembled comprehensive crosswalks of sample collection and ICFs in all ACTIV trials (included in the slides circulated before the meeting). Trial teams should review the crosswalk, note any measurement that is missing or misconstrued, and indicate which samples are not being banked (e.g., "blood for health check" samples [which refer to virologic blood levels used to screen patients] are generally not stored).

The ABPC's evaluation criteria will ultimately need to balance several competing sets of priorities. First, the ABPC must balance the desire to limit the number of platforms on which assays are performed—in order to prevent misleadingly conflicting results—with the need to validate results through some degree of duplication. A portfolio approach that approves only a small number of similar research studies may achieve this balance. Second, the ABPC must balance the goal of making samples available for pressing research with the interest in preserving some samples for unanticipated but valuable future use.

Any public-facing description of this effort (including its announcement and submission platform) should emphasize that protocol-defined analyses take precedence over all other uses of samples and thus that the ABPC cannot guarantee that samples will be available even for submissions that are evaluated positively. In addition, because controls are shared across arms of ACTIV trials, there are fewer control samples than investigational samples and thus the availability of control samples to external researchers may be limited.

Implications of Evolving Standard of Care

Outpatient Trials (ACTIV-2)

Results from outpatient clinical trials have begun to be published with potential implications for ongoing clinical trials. Single mAbs and nAb cocktails have shown impact on viral load, symptom scores, and hospitalization and death, leading Eli Lilly to announce that it will no longer conduct placebo-controlled trials of its current agents in high-risk patients (although the company has not decided how it will proceed instead). The anti-inflammatory colchicine has also shown some effect. However, it is not clear that sufficient evidence has emerged for regulators to establish any treatment as outpatient standard of care (SOC), particularly given the emergence of new variants that may challenge even promising therapies.

ACTIV-2 is relying on the NIH COVID-19 Treatment Guidelines Committee to make a recommendation before replacing placebo-controlled trials with comparisons to SOC. The team recognizes that other guidelines (including international guidelines) may emerge that put pressure on this decision. This pressure is unlikely to come from mAbs, based on the difficult logistics of their delivery, but perceptions of an oral drug such as colchicine may shift the randomized clinical trial landscape.

Anti-Inflammatories in Inpatients (ACTIV-1)

ACTIV-1 randomizes patients to SOC plus placebo or SOC plus investigational drug, with SOC typically consisting of remdesivir and dexamethasone. In response to recent publications on tocilizumab and other IL-6 inhibitors, approximately half of ACTIV-1 sites have added this drug to their SOC in patients who are on or about to begin ventilation. This development poses several issues for ACTIV-1: first, patients who have already taken tocilizumab are excluded from the ACTIV-1 trial, posing potential issues for recruitment; second, the potential use of three immunomodulators in the investigational drug arm raises safety concerns; and third, the changing treatment in the placebo arm will affect sample sizes and analyses. These issues may be magnified if sites begin to liberally define their "sickest" patients, as has occurred with dexamethasone. To avoid raising safety issues, ACTIV-1 could treat tocilizumab as a placebo (i.e., the drug would not be part of SOC in the investigational drug arm), but that would require a change to study design.

Anticoagulants in Inpatients (ACTIV-4A)

Dr. Judith Hochman presented pre-publication DSMB-reviewed data from ACTIV-4A (which she noted is not from a locked database and has not been peer-reviewed). The results somewhat counter-intuitively suggest that therapeutic anticoagulants provide benefit to moderate state patients who are hospitalized but do not require organ support care, but they do not help and may in fact harm severe state patients who do require ICU-level organ support. Dr. Hochman emphasized that these surprising results underline the fact that RCTs are necessary to identify treatments that can be confidently used to blunt the impact of COVID-19.

Overview

ACTIV-4A is designed to test the hypothesis that in hospitalized patients with confirmed COVID-19, therapeutic anticoagulation would safely improve clinical outcomes. The trial has generated results quickly because it is a combined effort of three platform trials—ACTIV-4; Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP); and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)—which have collectively (b) (4) [redacted].

Study Design

Each of the three partnering trials is a randomized, open-label, adaptive Bayesian trial that uses similar endpoints, protocols, and outcome measures in order to easily combine and evaluate data. The intervention is a therapeutic low molecular weight heparin or unfractionated heparin dosed according to hospital policy for venous thrombotic events (VTEs) and the control arm is standard prophylactic care. Patients were treated for 14 days or until discharge. The primary outcome is organ support-free days (OSFDs), which is an ordinal scale combination of organ-support free days through day 21 and in-hospital mortality at any point; organ support is defined by need for ICU-level care (e.g., mechanical ventilation, vasopressors, or high-flow oxygen; high-flow oxygen requirements were defined as 20 to 30 liters). The secondary outcomes for safety are major hemorrhage and heparin-induced thrombocytopenia (HIT) and for efficacy are mortality, intubation, major thrombosis, pulmonary embolism, VTE, stroke, myocardial infarction, and length of stay.

Patients are stratified by COVID-19 severity (moderate is defined as hospitalized but not requiring ICU level of care and severe is defined by requiring ICU level of care and organ support) as well as by D-dimer level (high, low, or unknown). Adaptive design decision rules declared superiority if findings showed a 99 percent probability of superiority on primary outcome and declared futility if the findings displayed a less than 5 percent probability of at least 20 percent improvement for primary outcome.

Preliminary Results and DSMB Futility Assessment

A statistical analysis committee extracted primary outcome data from all trials and presented a single report to the three ACTIV-4A DSMBs, which conducted a December 2020 futility

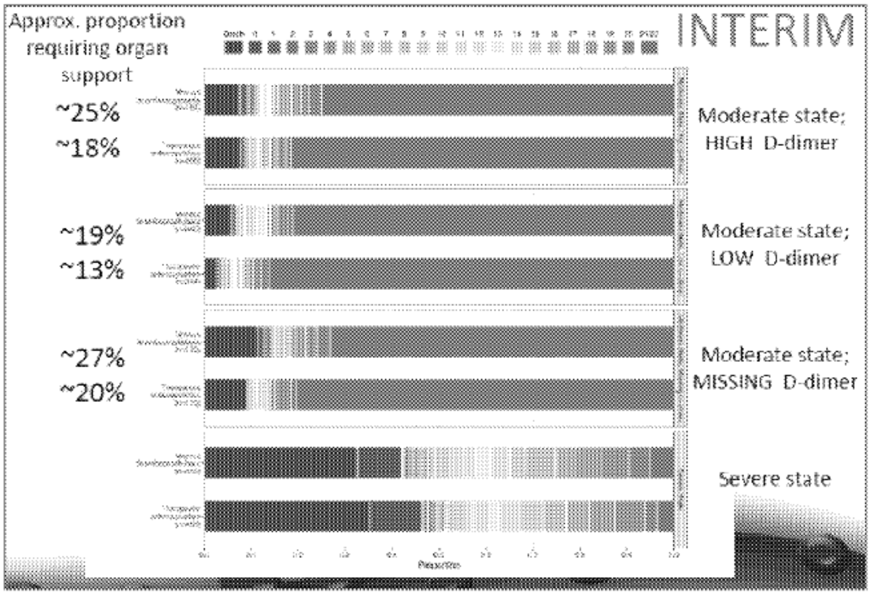


Figure 2

assessment (secondary safety data were also synthesized). The DSMBs recommended discontinuing enrollment of *severe state patients for futility* and recommended discontinuing enrollment of *moderate state patients in both D-dimer strata for superiority*. Further analyses showed that for the primary outcome of OSFDs, both the high and low D-dimer moderate patient groups displayed a 99 percent superiority probability (odds ratio of 1.57 for low and 1.53 for high D-dimer), while the severe state group displayed a 98 percent posterior probability of inferiority (see Figure 2).

Approximately 1.6 percent of moderate patients and 3.7 percent of severe patients receiving therapeutic anticoagulant displayed major bleeding; however, these results are preliminary, unadjudicated, and potentially subject to reporting bias. In addition, both moderate and severe patients receiving therapeutic anticoagulant displayed fewer thrombotic events, than those receiving prophylactic anticoagulant doses; however, these results may be impacted by increased mortality and organ support requirements in the severe patient group.

Discussion

Dr. Scott Berry clarified that most data aligned across the three platform trials in ACTIV-4A; adjustments were required for relatively minor issues, such as frequency of data collection (ACTIV-4 and ATTACC collect data daily and REMAP-CAP does so hourly). The ACTIV-4A team does not know why therapeutic anticoagulants have inverse efficacy in relation to disease severity. Dr. Hochman speculated that extensive microvascular thrombosis may lead to intrapulmonary hemorrhage in severe patients that cannot be treated by heparin. Because platelets and megakaryocytes have been implicated in COVID-19-related thromboses, P2Y12 inhibitors are also being added to ACTIV-4A.

Appendix A: Participants List

TRIAL TEAM MEMBERS

ACTIV-1

William G. Powderly, MD, *ACTIV-1 Chair and J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Sam Bozzette, MD, PhD, (not in attendance) *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Lisa LaVange, PhD, (not in attendance) *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

ACTIV-2

David (Davey) Smith, MD, *ACTIV-2 Chair Professor of Medicine, U. California, San Diego*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Michael Hughes, PhD, (not in attendance) *Professor, Department of Biostatistics, Harvard University*

Cyrus Javan, MD, MPH, *Medical Officer/Program Officer, Division of AIDS, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

ACTIV-3

James D. Neaton, PhD, *ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen*

Birgit Grund, PhD, *Associate Professor of Statistics, University of Minnesota*

ACTIV-4

Judith S. Hochman, MD, *ACTIV-4A Chair and Harold Snyder Family Professor of Cardiology, Department of Medicine, NYU Grossman School of Medicine*

Paul Ridker, MD, *ACTIV-4B Chair; Senior Physician, Brigham and Women's Hospital; Eugene Braunwald Professor of Medicine, Harvard Medical School*

Tom Ortel, MD, PhD, *ACTIV-4C Chair and Chief, Division of Hematology, Department of Medicine, Duke University*

Scott Berry, PhD, *Adjunct Professor, Department of Biostatistics & Data Science, Kansas University Medical Center*

Jean Connors, MD, (not in attendance) *Associate Professor, Department of Medicine Brigham and Women's Hospital*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI, NIH*

Eric Leifer, PhD, *Mathematical Statistician, NHLBI, NIH*

Allison Morris, MD, *ACTIV-4D Co-Chair and Professor of Medicine, Immunology, and Clinical and Translational Research, University of Pittsburgh*

Frank C. Sciurba, MD, *Professor, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh*

Abdus Wahed, PhD, (not in attendance) *Professor, Department of Biostatistics, University of Pittsburgh*

Clinton B. Wright, MD, *Director, Division of Clinical Research, National Institute of Neurological Diseases and Stroke (NINDS), NIH*

ACTIV-5

John Beigel, PhD, (not in attendance) *Division of Microbiology and Infectious Diseases, NIAID, NIH*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases*

OPERATION WARP SPEED

Tom Stock, DO, *Clinical Advisor to ACTIV-1 and Former Vice President, Clinical Development and Operations, Pfizer*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, (not in attendance) *Clinical Advisor to ACTIV-3 and Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

David Douglas, *Clinical Advisor to ACTIV-4 and Former Head, Global Research and Development Project Management Office, Pfizer*

Ciaran Lawlor, PhD, (not in attendance) *OWS Consultant, Boston Consulting Group*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Sheri Parker, PMP, PhD, *CAPT, MSC, USN, Therapeutics Clinical Operations Director, Operation Warp Speed*

Ritika Philip, (not in attendance) *OWS Consultant, Boston Consulting Group*

Col. Deydre Teyhen, *DPT, PhD*, (not in attendance) *Director of Therapeutics, Operation Warp Speed*

TX-CLINICAL WORKING GROUP

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-Chair)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

OTHER INVITED ATTENDEES

Cynthia Boucher, MS, *Clinical Trials Specialist, NCATS*

Kevin Bugin, PhD, (not in attendance) *Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)*

Krishna Deepak, MS, (not in attendance) *Consultant, Boston Consulting Group*

Nancy Geller, PhD, (not in attendance) *Director, NHLBI Office of Biostatistics Research, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Raahul Ramakrishnan, MD, (not in attendance) *Project Leader, Boston Consulting Group*

Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems*

Austin Van Grack, MS, (not in attendance) *Committee Coordinator, Social and Scientific Systems*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

STAFF

Evan Appell, *Consultant, Deloitte*

Alex Sorosa, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Jens Lundgren to Everyone: 09:22 AM

B.1.351 and B.1.28 carries mutations that may reduce the Lilly nMAb's neutralisation effects it appears (preprint from Ho et al) - Davey: your thoughs ? Thanks, Jens

From Davey Smith (he/his) to Everyone: 09:23 AM

Yes, it looks very clear that the mAbs will be impacted by variants and Lilly got knocked off early, and the South AFrican variant will knock off more

From Jens Lundgren to Everyone: 09:52 AM

well done Judy

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials, discussed other topics elevated for its consideration, and reviewed the status of several agents that have been reviewed by the Agent Selection Committee (ASC).

Dr. (b)(6) also provided the TOC with a general update on efforts to both sequence and test emerging SARS-CoV-2 variants. Dr. (b)(6) requested that the TOC receive periodic updates on these efforts so that it can account for the results of these activities in its agent prioritization and trial management efforts.

Trial Accrual and Status Updates

The TOC received updates on ACTIV-2 and ACTIV-3 accrual and onboarding of new agents.

ACTIV-2

ACTIV-2 has activated 89 sites and (b)(4). As of January 5, 2021, new patients are being enrolled to the (b)(4) study arm. The ACTIV-2 team expects to cease enrollment for the open-label study on January 15 and is working to finalize Version 3 of its protocol and to assess what caused previous delays in activating Version 2.

ACTIV-3

ACTIV-3 has reopened to begin testing (b)(4) agents. It has activated 29 sites and (b)(4). Patient enrollment rates per open site are higher than projected and the study team anticipates opening additional sites before the week of January 11. ACTIV-3 had its first Version 2 post-enrollment DSMB meeting on January 4, 2021. This meeting followed the reporting of two allergic reactions among trial participants, which were handled well, and DSMB members approved continuing the study. The ACTIV-3 team expects by mid-to-late January to have (b)(4) into Version 2 of the protocol; this milestone will enable the DSMB to conduct its interim futility assessment.

The ACTIV-3 team is working to finalize Version 3 of its protocol to begin testing (b)(4) agent. However, further discussion with FDA is needed about the wording of informed consent clauses regarding vaccine administration among trial participants (these issues are summarized under Topics for Discussion below). A subset of the ACTIV-3 team is working to finalize Version 3a of the protocol to test the (b)(4) agent in a factorial design with arms that do and do not include remdesivir.

Discussion

(b)(4) issued a press release during the week of December 28, 2020 reporting data from its inpatient trial. The ACTIV-3 team members confirmed that these data will not impact their trial.

Topics for Discussion

The TOC discussed several topics escalated for its consideration.

Protocol Language Surrounding Timelines for Participant Vaccination

The ACTIV-2 team has asked that the TOC finalize standardized language, to be used across all ACTIV master protocols, stipulating the length of time trial participants should wait after they have been administered a neutralizing antibody (nAB) before receiving a SARS-CoV-2 vaccine. Existing CDC language recommends a 90-day wait, which Dr. (b)(6) suggested adopting for ACTIV master protocols as well. Other TOC members agreed but highlighted the need for more data to inform these decisions. Dr. (b)(6) noted that the ACTIV-2 team has been working to launch its own vaccination sub-study to generate those data, and Dr. (b)(6) noted that Operation Warp Speed (OWS) has formed a Working Group to study this issue. Dr. (b)(6) also added that CDC, FDA, and NIH are developing standard guidance for vaccinating individuals who have received nAbs *until further data are available*, at which point this guidance will be suitably revised.

Studying Patients Who Are Infected After Receiving First Dose of Vaccine

The TOC agreed that ACTIV-2/-3 should not exclude patients who are infected with SARS-CoV-2 after receiving a first dose of vaccine but before receiving a second dose (assuming they meet all other criteria for inclusion in the trial). The TOC also agreed that ACTIV protocols should give guidance to these patients to wait 90 days post treatment before receiving any additional dose of vaccine (aligning with guidance given to all other trial participants). Dr. (b)(6) emphasized the importance of capturing patients' prior vaccination history in the studies' case report forms (CRFs) so that the information can be analyzed later.

Creating a Table Comparing nAbs Being Studied for the DSMB

The ACTIV-2/-3 DSMB has recently requested a table comparing attributes of the various nAbs being studied, and Dr. (b)(6) asked the TOC whether it recognizes a benefit in producing such a table. Dr. (b)(6) questioned its value, noting that certain key data elements (e.g., *in vitro* and *in vivo* neutralization data) would not be the result of head-to-head comparisons, and might therefore represent differences in assay performance or other factors as opposed to real differences between antibodies. Dr. (b)(6) and Dr. (b)(6) agreed that it would suffice to create a limited table (e.g., a pared down version of the "Simplified Crosswalk of nAb" table), representing only the antibodies currently being tested, for the DSMB to consult.

Drs. (b)(6) will meet to discuss what information to include in this table once they have received the summary of the DSMB meeting where this issue was raised.

Assessing Success of Site Recruitment Efforts

To help assess the success of earlier efforts (e.g., by (b)(4)) to accelerate the rate of site enrollment for ACTIV-2/-3, FNIH will compile a list of sites generated by these efforts so that it can be cross-referenced with (b)(4) s data on current enrollment and site activation status. Dr. (b)(6) will send a completed list to Dr. (b)(6) to be forwarded to (b)(4)

Agent Reviews

The TOC discussed the status of two agents reviewed by the ASC during December 2020 ((b)(4)

TOC members also briefly discussed the status of two previously reviewed agents from (b) (4). They stressed the need to discuss with (b) (4) its reasons for pausing enrollment of its trial in October 2020 to help inform ACTIV decisions about onboarding (b) (4) However, TOC members (b) (4) is unwilling to share its data, then its agent should be removed from consideration for testing in ACTIV-2/-3. Dr. (b) (6) will contact (b) (4) to revisit the ACTIV-3 request for further data on (b) (4)

Dr. (b) (6) suggested that the ASC/TOC consider reviewing the (b) (4)’. Dr. (b) (6) requested that Dr. (b) (6) provide her with the contact information for representatives from the company so that they can be solicited to submit their agent for ACTIV's official review.

(b) (4)

After receiving additional data and FDA feedback from (b) (4) on its (b) (4), the ASC recommended advancing this agent for testing, contingent on review of the agent's pending preclinical safety data (i.e., toxicity and cross-reactivity) as well as of its pharmacodynamics, pharmacokinetics, and Phase I test data.

The TOC endorsed the ASC's recommendation to approve this agent for entry into ACTIV-2/-3 and for (b) (4) representatives to begin working immediately with the ACTIV-3 trial team to start agent onboarding. ACTIV-2 does not have capacity to begin onboarding this agent immediately, but it might be able to do so during the next several months. Dr. (b) (6) will deliver these updates to (b) (4) representatives and will gauge their willingness to have their agent tested at sites that are not within the United States, which may accelerate ACTIV-2's ability to onboard the agent.

(b) (4)

The ASC concluded that (b) (4) should conduct preclinical testing on its (b) (4)—as suggested by FDA—before ACTIV-2/-3 consider the agent for entry into trials. The TOC accepted the ASC's conclusion. FNIH will ask (b) (4) representatives how long it will take to complete the requested preclinical testing.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

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Rachel Harrigan, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

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Helen Q. Chen, *Consultant, Deloitte*

Evan Appell, *Consultant, Deloitte*

Alex David Sorosa, *Business Analyst, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) met to receive ACTIV-2 and ACTIV-3 updates, discuss topics escalated for TOC discussion, and view a presentation on ACTIV-3's envisioned study design for (b)(4)

Trial Status Updates

ACTIV-2

ACTIV-2 is transitioning to its (b)(4) neutralizing antibody (Ab). Approximately 30 sites are enrolling patients for the open label study; enrollment rates are slower than expected, potentially because of the Thanksgiving holiday.

Version 2 of ACTIV-2 is under review at FDA, and the team expects to receive a decision to proceed imminently. Version 2 will integrate the (b)(4) monoclonal Ab cocktail into ACTIV-2, in a study arm that should begin by mid-December 2020.

ACTIV-2's next Clinical Science Review Committee (CSRC) review will occur on December 10, at which time multiple products will be reviewed for potential addition to Version 3 of the protocol. Dr. (b)(6) expressed doubt that SAB's product will be ready for review during the December 10 meeting (discussion of this issue is summarized below under Topics for Discussion).

Discussion

Dr. (b)(6) noted that the racial/ethnic diversity of ACTIV-2 patients seems to be dropping, but Dr. (b)(6) clarified that the apparently diminished percentages of Black patients has resulted from an update to a more granular method of classifying these patient groups. Dr. (b)(6) noted that the category "Ethnicity" on Dr. (b)(6) slide should be updated to "Race" and "Ethnicity" should instead name the category currently labeled "Hispanic or Latino"). Dr. (b)(6) will update her slides accordingly.

ACTIV-3

ACTIV-3 is paused and therefore has no accrual updates to report. Registration and opening of sites will renew soon (perhaps next week), pending FDA/central IRB approval of Version 2 of the protocol, which will include (b)(4) . The ACTIV-3 team has also created an Appendix to integrate (b)(4) combination Ab into a future iteration of the trial.

ACTIV-3's first paper is in press at the *New England Journal of Medicine.*

Topics for Discussion

Integrating the (b)(4) Agent into Version 2 of ACTIV-2

Operation Warp Speed (OWS) leadership has been tracking (b)(4) s agent and would like it to be integrated into Version 2 of the ACTIV-2 protocol, which would require that its Ab be reviewed during the December 10 CSRC meeting. The ACTIV-2 team has expressed doubt that (b)(4) s Ab will be ready for review by December 10. Dr. (b)(6) explained that the ACTIV-2 team received (b)(4)'s Phase 1 data on November 25, the day before Thanksgiving, and rushed to create an appendix for the company's agent. That appendix was submitted to (b)(4) on Monday, November 30 with questions that (b)(4) has not yet addressed. The ACTIV-2 team and (b)(4) have a call scheduled for Thursday, December 3, during which some of these questions might be answered. However, Dr. (b)(6) stressed the unanswered questions are important and that the likelihood of resolving them all and finalizing the appendix before the CSRC meets on December 10 seems remote. However, Dr. (b)(6) confirmed that the CSRC could hold a separate meeting after December 10 (potentially the 17th) specifically to review the (b)(4) agent.

In preparation for the ACTIV-2 team's call with (b)(4) on December 3, Dr. (b)(6) will draft a list of remaining gaps/questions that need to be addressed before the CSRC conducts its final review, so that the ACTIV-2 team can review that list with (b)(4) and strategize on timing moving forward. Dr. (b)(6) will ensure that the invite for the ACTIV-3 (b)(4) meeting includes (b)(6) and (b)(6) so that labeling and supply issues can be fully discussed.

Discussion

Dr. (b)(6) noted his support for integrating (b)(4) agent into ACTIV-2 by mid-January (the initially envisioned timeline) but expressed reservations about onboarding another agent into ACTIV-2 during December. Four new agents are already entering the trial before 2021 and the holiday season may lower accrual rates. Dr. (b)(6) confirmed that the goal is not to activate (b)(4) before 2021, but to hold to the original timeline of mid-January.

Immune Modulators for ACTIV-2

Dr. (b)(6) informed the ACTIV-2 team representatives that ACTIV's Immune Modulator Subteam compared (b)(4) the most promising of the three compounds. It decided, just before Thanksgiving, to refer (b)(4) to the ACTIV-2 team for consideration. Dr. (b)(6) emphasized that the ACTIV-2 team will need to know the status of any potential Phase III studies that have been conducted for (b)(4).

Dr. (b)(6) also noted that (b)(4) are still under consideration. Dr. (b)(6) noted that the (b)(4) may have prioritized (b)(4) for its studies, and that ACTIV should confirm whether that is the case to avoid duplicative efforts.

TOC members expressed interest in receiving brief updates from Dr. (b)(6) every two weeks on which agents the various prioritization teams have decided *not* to pursue.

ACTIV-3's (b)(4) Study Design (Open Session)

Dr. (b)(6) of NHLBI's PETAL Network joined the TOC meeting to present on the ACTIV-3 study plan for (b)(4)–i.e., (b)(4)—which is expected to have Phase II data readouts from a randomized controlled trial of 144 patients by mid-January. NHLBI/NIAID representatives are working with ACTIV-3 to draft a trial protocol with a factorial design using (b)(4), intending to enroll first patients within a week of the Phase II readout if the results are positive. This draft is agnostic on whether the new study should be written as an appendix or as a sister protocol to the existing ACTIV-3 study.

Discussion

Dr. (b) (6) confirmed that neither the ACTIV-1 nor the ACTIV-5 teams have the capacity to integrate (b) (4) into their studies at present.

At Dr. (b) (6) s inquiry, Drs. (b) (6) and (b) (6) confirmed that the TOC has the authority to vote on the proposed ACTIV-3 factorial design of the (b) (4) study with remdesivir. Dr. (b) (6) emphasized that clinicians are unsure of whether severely ill COVID-19 patients on mechanical ventilation should be treated with remdesivir and proposed soliciting further input from NIAID experts. Drs. (b) (4), (b) (6) both endorsed the envisioned factorial design with (b) (4), and Dr. (b) (6) advocated for consulting with Dr. (b) (6) of ACTIV-5 before taking a final vote—because Dr. (b) (6) has extensive experience with (b) (4) in COVID-19—and specifically suggested that the TOC receive a written proposal to react to. Dr. (b) (6) will follow up with the trial teams on Friday, December 4, and bring a written proposal to the TOC for consideration (perhaps by mid-December) if the ACTIV-3 team agrees to study (b) (4). Dr. (b) (6) also clarified that a protocol synopsis has been written and can be shared; Dr. (b) (6) agreed that it would be helpful to review that document.

Co-Enrollment between ACTIV-3 and ACTIV-4 at Sites with Both Trials

Dr. (b) (6) requested that Dr. (b) (6) raise the potential issue that co-enrollment between ACTIV-3 and ACTIV-4 at sites running both trials could threaten funding guarantees for participating CTSN and PETAL sites. Dr. (b) (6) will raise this discussion during the Cross-Trial Leadership meeting on Friday, December 4.

Timeline

Dr. (b) (6) has updated the agent onboarding timeline to reflect the expectation that (b) (4)'s agent is expected to enter ACTIV-3 during January 2021.

Next Week Agenda

Dr. (b) (6) will add a discussion of (b) (4)'s logistical hurdles to next week's TOC meeting agenda.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Elizabeth Church, PhD, *Deputy Director, Therapeutics Research Program, Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH*
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Samuel Brown, MD, *Associate Professor, University of Utah School of Medicine*
William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*
Rachel Harrigan, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Col. Deydre Teyhen, DPT, PhD, *Director of Therapeutics, Operation Warp Speed*
Austin Van Grack, MS, *Committee Coordinator, Social and Scientific Systems*

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Helen Q. Chen, Consultant, Deloitte
Hana Nasr, MPH, Consultant, Deloitte

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) met to receive ACTIV-2 and ACTIV-3 updates, discuss topics escalated for TOC consideration, and revisit a recent decision to test (b)(4) [redacted].

Trial Status Updates

ACTIV-2

ACTIV-2 has 78 sites open and (b)(4) [redacted] (i.e., patient enrollment has accelerated).

The NIAID Clinical Science Review Committee (CSRC) will meet on December 10 to consider four agents: two (b)(4) [redacted]. If the agents are approved to proceed by CSRC, they will be sent to FDA for review, as appendices to Version 3 of the ACTIV-2 protocol. However, Dr. (b)(6) [redacted] noted that (b)(4) [redacted] has not yet signed its clinical trial agreement (CTA), which could delay the process. Dr. (b)(6) [redacted] agreed to follow up with the relevant parties to encourage timely signing of the CTA.

ACTIV-3

ACTIV-3 remains paused; Version 2 of the protocol will launch during the week of December 14 to test (b)(4) [redacted] Dr. (b)(6) [redacted] reported the possibility that the (b)(4) [redacted] agent would expire while Version 2 of ACTIV-3 is ongoing—in which case randomization to the (b)(4) [redacted] agent would cease temporarily. The ACTIV-3 team expects that, if this issue arises, it will be resolved by the middle/end of January 2021.

The manuscript reporting on ACTIV-3's first trial is scheduled to be published on December 22.

Topics for Discussion

Funding Future Versions of ACTIV-2/-3

Dr. (b)(6) [redacted] noted that Operation Warp Speed (OWS) will discontinue in 2021, which will remove ACTIV's current source of funding for its trials. She stressed the need to plan for this transition to ensure that ACTIV trials receive the support they need to pursue their study plans. Specifically, (b)(6) [redacted] recommended that the trial teams across the entire ACTIV clinical trial portfolio develop projections of what funds they expect to need over the next year so that NIH Institutes (e.g., NIAID, NHLBI, and NCATS) and FNIH can produce a strategy to obtain those funds from the U.S. Congress, potentially with assistance from the Biden transition team. ACTIV clinical trialists should develop different funding scenarios (e.g., an effective vaccine becoming widely available during the first half of 2020) that could be added as line items to NIH's appropriations as part of its pandemic response budget.

Dr. (b)(6) [redacted] recommended that Dr. (b)(6) [redacted] be involved in coordinating these efforts among NIH Institutes. Dr. (b)(6) [redacted] will contact the leaders of all ACTIV trials, and of the networks they are using, to facilitate development of these projected funding scenarios. Dr. (b)(6) [redacted] and (b)(6) [redacted] will also discuss this plan with Dr. (b)(6) [redacted] during a meeting on December 11.

(b)(6) reported that he has described to Biden transition team representatives the concerns about future ACTIV funding summarized above and confirmed to them that ACTIV has no immediate need for further funds but that a strategy is needed to ensure sustainable funding through 2021. (b)(6) advised transition team member Dr. (b)(6) to confer with NIH and OWS to facilitate development of such a strategy, and Dr. (b)(6) praised ACTIV's efforts, committing to pursue sustained funding for the partnership.

Interactions with Biden Transition Team

FNIH leadership met with the Biden transition team on December 3 to discuss ACTIV's efforts. Transition team representatives included Drs. (b)(6) In preparation for the meeting, FNIH sent these representatives a summary of ACTIV's efforts thus far, and then fielded questions on these efforts during the meeting. Dr. (b)(6) expressed concern about ACTIV's focus on nAbs, but (b)(6) assuaged his concerns by describing the ACTIV agent prioritization process and OWS efforts to scale for Ab production and distribution. Dr. (b)(6) raised concern about low rates of trial enrollment; (b)(6) described ACTIV's efforts to improve its trial enrollment rates, which transition team representatives found encouraging.

More broadly, transition team representatives emphasized the need to improve messaging to the country to address vaccine and therapeutic hesitancy and the importance of the scientific response to the pandemic. They also stressed that, once the exigencies of the current pandemic have passed, it will be crucial to catalog lessons learned and to apply them to prepare for future pandemics. Another major theme of discussion was the need to reform and improve the clinical trial system in the United States. Meeting attendees suggested investing more in incorporating community sites—especially in underserved minority communities and rural areas—into clinical trial networks.

Discussion

Dr. (b)(6) has expressed several concerns about ACTIV's clinical trials, and Dr. (b)(6) who has a preexisting working relationship with Dr. (b)(6) offered to connect with him to provide him with more detail on ACTIV's trials and to address his concerns, such as ACTIV-2 enrollment rates and number of agents being tested. (b)(6) and Dr. (b)(6) approved of this action.

Design Plans for ACTIV-3 Version 3

The TOC strongly endorsed the ACTIV-3 team's plans to wait for readouts from the (b)(4), (b)(5) trial before proceeding with testing this agent in ACTIV-3 version 3. If testing for this agent proceeds, the ACTIV-3 team envisions randomizing patients to one of three trial arms: (1) (b)(4), (b)(5) factorial. However, although (b)(4), (b)(5) is current standard of care, uncertainty about whether it might have undesired effects for high-flow/mechanically ventilated patients is a serious consideration and more data are needed to determine whether remdesivir is safe for these patients. Participants emphasized that standard of care is evolving quickly and that it would be useful to obtain input from the larger TX-Clinical WG on addressing these questions in Version 3 of ACTIV-3. Dr. (b)(6) will reorganize the agenda for the TX-Clinical WG meeting on December 10 to make room for this discussion, which will be facilitated by Dr. (b)(6) [redacted].

(b)(4) [redacted] for ACTIV-2

The TOC recently expressed interest in testing (b)(4) [redacted] in ACTIV-2, but the submitting group to ACTIV has obtained funding to study the agent in 880 patients. The trial will be conducted virtually, which will not enable collection of patient samples or biomarkers that would be crucial to studying the agent's mechanism of action. The TOC agreed to cease pursuing (b)(4) [redacted] to avoid spending its resources duplicating an ongoing confirmatory trial of the agent. Dr. (b)(6) [redacted] will request that the Principal Investigator of the external trial provide her with semi-weekly updates on enrollment status (because if ACTIV decides not to pursue (b)(4) [redacted] because it would duplicate another trial, it needs to confirm that the other trial is adequately enrolling).

Estimated Product Timelines

Dr. (b)(6) [redacted] presented updated timelines for agent entry into ACTIV-2 and ACTIV-3, shown below.

(b)(4), (b)(5) [redacted]

TOC Meeting Next Week

Next week, the TOC will spend approximately half of its meeting discussing what data are being generated by independent laboratories on the various Abs under consideration, and how those data are to be assessed. Dr. (b)(6) [redacted] reminded the TOC that companies agreed to have their agents tested in independent laboratories with the expectation that data generated would not be used to (de)prioritize their agents for entry into ACTIV trials, and that those agreements should be honored. Dr. (b)(6) [redacted] asked that the conditions of those initial agreements be clarified for the TOC during its discussion next week.

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Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems Inc.*

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Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix A: Chat Log

David Goff, NHLBI: 21:54

trials of Long COVID treatments may also be important to consider in this context.

Libby Higgs: 44:03

However, I am a bit concerned about the quality of the data in the company trial.

Janet Woodcock M.D. "Operation Warp Speed": 45:11

AGree, that is why it would just be a stage gate, if their trial is negative we maybe should not pursue but it a "lean" we should consider evaluating it. jw

David Goff, NHLBIL: 54:19

much appreciated

Libby Higgs: 01:08:46

I did not know that

Libby Higgs: 01:09:01

Is that in the CTA/MTA?

Erica Ollmann Saphire: 01:09:51

in standardized platforms

ACTIV, Cross-Trial Operations Meeting

Thursday; January 28th, 2021

Action Items

Action Items		
	Information	**Owner(s)**
1.	Include the number of patients enrolled as well as the target number of patients for each (hyper immunoglobulin) trial in the next iteration of this deck.	**Stacey Adam**
2.	Let Linda Silverstein know the data from the Medscape campaign (from the website and call center)	**Bill Erhardt**
3.	Let Linda Silverstein know call center traffic data	**Chris Shreeve**

Meeting Summary

- ACTIV-2, V3.0 and ACTIV-3, V3.0 have received Safe-to-Proceed.
- ACTIV-2: (b)(6) open label is now closed (as of 01/05); everything is now currently being randomized to Brii while the sites are working to get version 3.0 open
- Slight delay of ACTIV-4c → launch date looking to be mid-February
- Potential "ACTIV-6": ACTIV is exploring the feasibility of establishing an outpatient, pragmatic platform trial to evaluate generic and widely available drugs
- THANK YOU to Rachel Harrigan (hope to see you again soon as a medical officer) and Sheri Parker – you will be missed!! ☺
- AWS is now renamed to USG COVID Therapeutics Response Team.

Notes

Agenda

- Opening and Welcome
- ACTIV Trial Status Updates
- IQ Solutions Listening Sessions – Lessons Learned
- Pragmatic Platform Trial Update
- Meeting Recap

ACTIV Trial Status Updates
(Stacey Adam)

- ACTIV-1: 33 sites open; (b)(4) as of 01/27
    - Team is reviewing FDA comments on Version 2.0 and SAP
    - Team is reviewing DSMB comments on safety monitoring; everything is safe to move forward
    - Evaluating and selecting participating sites
    - Thomas Stock:
        - Salient lines of discussion for ACTIV-1 recently → having a strategy to manage the anti-IL6 issue relative to some of the data that's recently emerged; anxiously

awaiting (if there is any) update to NIH guidelines in assessing impact to the ACTIV-1 trial

    - Challenge with CBC arm because of its investigational status and because it needs to be administered orally for 28 days; a lot of patients prefer not to be randomized to that arm

- ACTIV-2: 36 or 37 sites open; not 97 (due to the change-over from Version 1.0 to Version 2.0); (b)(4) as of 01/27 (69 patients on Brii)
  - (b)(4) open label is now closed (as of 01/05); everything is now currently being randomized to (b)(4) while the sites are working to get version 3.0 open
  - Version 3.0 received Safe-to-Proceed and expect FPI this week
  - Version 4.0 to be submitted to FDA this week; unique because it is not going to CDER → it's going to CBER because the polyclonal from (b)(4) is actually considered a biologic due to the generation in cows; slight delay because CBER has a mandatory 30 days (not as quick of a turnaround as CDER)
  - Team will be meeting with FDA on Feb. 11 on symptom-based endpoints
  - Bill Erhardt: had some conversations with ACTIV-3 to make the transition between versions as efficient as possible; any ideas are appreciated
- ACTIV-3: 38 sites open, (b)(4) as of 01/27
  - Held DSMB meeting on 01/25 to continue safety review
  - Version 3.0 received Safe-to-Proceed and expect FPI this week
  - ACTIV-3b/ TESICO submitted to the FDA on 01/19 (working with new division in FDA)
  - Libby Higgs: the ACTIV-3 comments from the DSMB have been right on target; they have asked the team for additional criteria around anaphylaxis
- ACTIV-4:
  - (4a) Hospitalized: 60 sites open; (b)(4) as of 01/27; first results on moderately ill patients released (not public yet)
  - (4b) Pre-hospitalized: 11 sites open; (b)(4) as of 01/27
    - Still awaiting final signature on contract with CVS; allowing CVS to become sites for them and expanding enrollment
  - Post-hospitalized received first drug shipment on 01/05
    - Slight delay/logistical challenges; looking at a mid-February launch date
- ACTIV-5 (Big Effect Trial): 10 sites open (target = 40 sites; identified 25 and working through the process with them); (b)(4) of 01/27
  - Identifying other sites; 16 more patients in process of enrollment
  - Assessing/ prioritizing additional investigational agents
- Convalescent Plasma Trials – enrolling well
  - CONTAIN COVID-19 (inpatient)
    - 19 sites open; (b)(4) as of 01/20 (target = 1,000 patients)
    - DSMB met on 01/22 to review data from the first 715 patients; received a Continue as Planned; next DSMB will be on 02/05
    - Adding up to 10 more sites; UT Rio Grande Valley enrolled first patient on 01/22

  - PassItONII (inpatient)
    - 22 sites open (adding up to 11 more); (b)(4) as of 01/27
    - DSMB met on Tuesday, 01/26 to review data from (b)(4) – waiting for recommendations; next DSMB to review 750 patient interim analysis is being rescheduled for mid-March
    - Adding up to 11 more sites; UChicago and UArkansas activated on 01/08
    - Rationale and design manuscript in preparation/ almost ready for submission
    - Sarah Dunsmore: As you add more patients, the missing data entry becomes more and more of an issue and establishing those workflows early between balancing enrollment needs, data entry needs, and preparation for the SMB meetings is very important. There has even been a pause on enrollment in this trial to get data entered; the quick turnaround on the next DSMB meeting is more about getting follow-up data entered than about getting new enrollment.
    - **There's going to be a lot of collaboration between CONTAIN COVID-19 and PassItOn; they're working with VA_CURES and FDA statisticians planning a meta-analysis.
    - **Road to the Plasma Summit – USG debrief on (b)(4) data is being scheduled. (b)(4) samples to be analyzed by (b)(4) – readout expected in late February.
  - C3PO (outpatient)
    - 51 sites; (b)(4) as of 01/27
    - Working with 65 sites to get them open
    - DSMB met on Tuesday, 01/19 to review sample size estimate based on total event rate from 300 patients (increased sample size to 900 patients based on meeting); next DSMB meeting is planned for 01/29 (the same 300 patients will be reviewed for safety)
    - Perhaps need to start collating information and have a template for the individuals on the operations side to look at and reference
  - Libby Higgs: there can potentially be a read-out in the next few weeks on the inpatient hyperimmunoglobulin trial
  - Lynn Marks: it may be helpful to include the target patient numbers for these (hyper immunoglobulin) trials

IQ Solutions Listening Sessions – Lessons Learned
(Linda Silverstein, IQ Solutions)

- Spoke about recruitment challenges and opportunities at the last meeting.
- Messaging Summary:
  - Even if you're hospitalized, you have options.
  - ACTIV studies are federally sponsored studies; not pharma studies – you can trust them.
    - Lynn Marks, Libby Hicks, and Rachel Harrigan: we need to be careful with the wording of this message as it may be suggestive of the fact that you canNOT trust pharma; these messages need to be vetted and the wording needs to change

  - ACTIV studies are the gold standard of the studies currently being done.
  - Participating in these studies could save your life.
  - If you have a family member in the hospital, ask about clinical trials.
    - Bill Erhardt: change "hospitalized" to "sick" for outpatient trials
    - Peter Kim: we would like a good distribution of patients that are early and late, so a message about joining trials as soon as you get sick would be a good addition; another important message to convey to the public is that the US government is evaluating the BEST POTENTIAL TREATMENTS OUT THERE
- Linda Silverstein:
  - What are some particular challenges with getting a patient's healthcare provider to discuss clinical trials with them?
    - Bill Erhardt: very hard to tell; in ACTIV-2, there has been a lot of outreach to physicians; in December, a Medscape campaign was started (paid advertising on Medscape – in order to go directly to primary care physicians) → we should be able to track this through our website and call center – Bill will let Linda know as soon as they have the data
    - Rachel Harrigan: Is there any messaging on the sense of civic duty?
    - Bill Erhardt: Will this material be IRB reviewed?
      - Yes, it will.
- Materials Summary:
  - Be sure materials are inclusive.
  - Utilize QR codes.
  - Videos for patient and HCPs are effective.
  - Patient testimonials are effective.
  - Bill Erhardt: Will the materials also be in Spanish?
    - Yes, they will.

Pragmatic Platform Trial Update
(Stacey Adam, FNIH)

- Potentially "ACTIV-6"
  - ACTIV is exploring the feasibility of establishing an outpatient, pragmatic platform trial to evaluate generic and widely available drugs (e.g., (b) (4) [redacted] etc.) for COVID-19 treatment
  - study design:
    - clear endpoints; simple and low-touch; estimated sample size = 1K+; gated structure to test short and long-term effects
  - progress to date: met with various networks/ organizations to discuss potential collaboration (b) (6) [redacted] FDA, NCATS all expressed interest to support
  - path forward: collecting and reviewing existing protocols from each of the four networks to serve as a starting point for the potential ACTIV-6 master protocol

        - Sarah Dunsmore: If this is stood up, would it become a part of this meeting?
            - Yes, it will.

CHAT

- **Lmcnay**: Apologies- I have a 930am meeting I will need to take.
- **Libby Higgs**: Thank you Sheri and Rachel!!!
- **Kevin**: Thank you, both! We will miss you
- **Lynn Marks**: All the best!!
- **Libby Higgs**: Yes, come back
- **Libby Higgs**: All I have another meeting I need to cover, Rachel will cover for ACTIV 3, thanks
- **Stacey Adam**: Thanks, Libby
- **Deydre Teyhen**: Agree - I think focusing on early enrollment/early treatment is a critical message.
- **Kevin**: Agree. We are about breakthroughs.
- **Lynn Marks**: Would suggest attention to the line indicating these studies could save your life as a bit too far in trying to persuade interest, especially since we don't note that they could also have a serious life threatening adverse event as a result of being in a study

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials and discussed other topics elevated for its consideration. Dr. (b) (6) also reported that the ACTIV-2/-3 Agent Selection Committee will not advance (b) (4) cocktail at this time but is requesting further data from (b) (4) to support another round of evaluation.

Trial Accrual and Status Updates

ACTIV-2

ACTIV-2 has activated 97 sites and (b) (4). The (b) (4) arm closed on January 15, so all patients enrolled since that date ((b) (4) so far) have entered the (b) (4) study arm and will continue to do so until Version 3 of the protocol is launched, likely in the beginning of February. A substantial proportion of all ACTIV-2 enrollees are Hispanic or Latino (31 percent), but only 7 percent of all enrollees are Black. Although efforts are underway to activate ex-U.S. sites, further discussion by the TOC may be needed to overcome delays.

Discussion

Dr. (b) (6) proposed tracking patient demographics separately for the (b) (4) study arm, and (b) (6) agreed. Dr. (b) (6) will contact (b) (4) to request more detailed data on patient enrollment demographics. Dr. (b) (6) noted that, once multiple agents are being tested in Version 3 of the protocol, ACTIV may need to request that (b) (4) alter its method of tracking patient demographics (i.e., to enable those data to be separated by study arm).

Dr. (b) (6) noted that the ACTIV-2 team must consider what implications standard of care for outpatient therapy may have for ACTIV-2 design (e.g., given preprint results from (b) (4) studies). The ACTIV-2 team will meet with FDA representatives on February 11 to discuss a proposed change-in-symptom endpoint for Phase III trials; if this endpoint receives FDA approval, the TOC will develop a strategy for disseminating it to external study teams.

The TOC generally agreed that, because the recently preprinted colchicine study stopped after enrolling (b) (4), rather than the originally planned 6,000, its results are not as robust or informative as the TOC had hoped they would be. Dr. (b) (6) will distribute the preprint report along with this meeting summary to TOC members.

ACTIV-3

ACTIV-3 has activated 38 sites and (b) (4). Version 2.0, which is ongoing, includes (b) (4) study arms. Version 3.0 will launch an (b) (4) study arm, likely in the beginning of February. ACTIV-3 patient demographics look promising (19 percent Hispanic and 22 percent Black).

Discussion

Dr. (b) (6) noted that 450 patients are needed to complete ACTIV-3's futility assessment and that the ACTIV-3 team expects to reach that milestone by February 11, enabling the DSMB to complete its futility assessment during its meeting on February 22, or, alternatively, March 1.

Dr. (b) (6) confirmed that recently obtained results from ACTIV-4a indicate that therapeutic dose heparin may have performed well enough to become standard of care, which could impact ACTIV-3's study design. The ACTIV-3 team is planning to discuss these results with ACTIV-4a's principal investigator to review the data in more detail, and if necessary, will revise the master protocol appendix describing standard of care for moderately ill inpatients. Impacts of recent and forthcoming trial results on the ACTIV master protocols' standards of care will be discussed during the next Cross-Trial Meeting.

Topics for Discussion

Potential Funding and Bandwidth Issues for ACTIV-3/-3b/-4a Sites

Dr. (b) (6) reported that some NIAID- and NHLBI-affiliated sites participating in ACTIV-3 and -4 have raised potential concerns about funding and bandwidth issues that could be interfering with cross-site collaboration. None of the NIAID or NHLBI representatives on the TOC were aware of any specific concerns, and Dr. (b) (6) agreed to investigate further and to report her findings back to the TOC so that any potential issues can be resolved as quickly and smoothly as possible. Dr. (b) (6) will also consult with his colleagues at NHLBI to determine what issues may have arisen in NHLBI clinical site networks.

Updates on Potential ACTIV-6 (Pragmatic Trial)

ACTIV is now exploring the feasibility of establishing an outpatient, pragmatic platform trial to definitively evaluate widely available generic drugs (e.g., (b) (4) for COVID-19 treatment potential. This simple study would have clear endpoints, approximately 1,000 patients/arm, and potentially a gated structure. ACTIV has met with various networks and organizations to discuss potential collaboration on this trial and has received many expressions of interest. Next steps are to collect and review all existing protocols from (b) (4) (b) (4) to serve as a starting point for the potential ACTIV-6 master protocol, and to coordinate broader discussions with key groups to determine agent prioritization criteria, detailed study design, roles and responsibilities, resources, and governance. ACTIV-6 is expected to launch initially within the U.S. only, but that expectation could change pending further discussion (e.g., of balancing regulatory hurdles vs. testing against global variants).

Participants generally agreed that an ACTIV-6 trial could be valuable but emphasized that it is crucial to coordinate with other groups to avoid duplication of efforts and to think carefully about the tradeoffs between testing more agents and obtaining rapid results. Dr. (b) (6) suggested establishing an early go/no-go criterion to safeguard against wasting resources. Dr. (b) (6) suggested using response-adaptive randomization in the ACTIV-6 study design and stressed the need to consider impacts of mid-trial vaccinations on the study's readouts.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID, NIH*

James P. Kiley, PhD, *Director, Division of Lung Diseases, NHLBI, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Gilbert (Lynn) Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Erica Ollmann Saphire, PhD, *Professor, La Jolla Institute for Immunology*

David (Davey) Smith, MD, *Professor of Medicine, U. California, San Diego*

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, *Director of Special Programs Staff, Office of New Drugs, FDA*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

Col. Deydre Teyhen, DPT, PhD, *Director of Therapeutics, Operation Warp Speed*

Austin Van Grack, MS, *Committee Coordinator, Social and Scientific Systems*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Helen Q. Chen, *Consultant, Deloitte*

Evan Appell, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

David Goff, NHLBI: 22:01

The COLCORONA manuscript is now posted on medRxiv:
https://medrxiv.org/cgi/content/short/2021.01.26.21250494v1

David Wholley: 56:39

Judy, the ivermectin trial you mentioned is being contemplated by the MRC as in Medical Research Council of the UK?

Libby Higgs: 57:31

The G7 is particularly interested in more collaboration with UK specifically reaching out to the US....Canada also interested in greater collaboration

Emily Erbelding: 58:06

re: MRC I am guessing its the South African MRC

Judith Currier: 58:07

Regarding MRC- I only heard they were planning a trial. I can try to get more info

Judith Currier: 58:25

Yes South African MRC

David Wholley: 58:48

Yes thanks please let me and Stacey know

High-Level Meeting Summary

The Vaccines Working Group (WG) invited Dr. Robert Gallo to present on his strategy to induce protection against COVID-19 infections through the dissemination of the oral polio vaccine (OPV), which is inexpensive, widely available, and safe. He proposed initiating both a clinical trial to assess the impact of OPV on SARS-CoV-2 and human challenge studies using influenza and seasonal coronaviruses.

The Vaccines Clinical Trials Subgroup presented the outcomes of its discussion regarding the implications of a first licensed vaccine on ongoing placebo-controlled trials. It recommended focusing on methods to shorten the time period between licensure and identification of correlates of protection for the first vaccine and to plan for the possibility of needing to adapt placebo-controlled trials, such as including active control for some populations.

Oral Polio Vaccine as a Method of COVID-19 Prevention Presentation by Dr. Gallo

Gaps in Current Vaccine Efforts

The majority of current COVID-19 vaccine clinical trials focus on candidates targeting viral spike proteins, with the goal of measuring neutralizing antibodies as a correlate of protection. However, this approach is still hypothetical because the correlates of protection for COVID-19 remain largely unknown. Dr. Gallo noted that the HIV vaccine research community has long sought to elucidate the general relationship between neutralizing antibodies and correlates of protection, but has not found significant evidence that such a relationship exists.

Furthermore, even if neutralizing antibodies are observed, they do not guarantee long-term disease protection. The experience is that antibody responses targeted to glycosylated proteins with mannose chains do not have provide long-term immunity. Dr. Gallo predicts that these antibodies will persist only 4 to 6 months after vaccination. Dr. Gallo and his colleagues at UMD's School of Medicine, Drs. Tony DeVico and George Lewis, are currently investigating whether the low durability of these antibodies is correctable; recent findings indicate that low durability may be related to B-cell maturation within bone marrow niches.

Dr. Gallo emphasized that the COVID-19 vaccine research community should diversify its vaccine candidates to ensure the field has alternative options if spike protein-based vaccines are not successful. Thus, he proposed the use of OPV to induce protection against COVID-19.

Non-Specific Protection of OPV

Vaccines induce both innate and adaptive immune responses. Innate immunity is an emergency response that involves interferon stimulation and occurs within hours, compared to adaptive immunity, which involves both antibody-derived and cellular responses and requires weeks to months to take effect. Further, vaccines that induce innate immune responses, like OPV, result in longer durability of protection (i.e., months to 1 year post-vaccination). By contrast, whereas vaccine-based adaptive immunity is thought to be both durable and virus-specific, durability of the response is not guaranteed.

The only vaccines that can induce innate immune responses are live virus vaccines. The non-specific benefits of a live virus vaccine were first demonstrated by the Bacille Calmette-Guérin (BCG) vaccine for tuberculosis (TB) disease in the 1940s and second by OPV in the 1950s. OPV was subsequently deployed to control unrelated (non-polio) pathogens in Russia and Singapore and was tested on adult volunteers during a later influenza outbreak in Russia; in the latter study, volunteers that received OPV displayed a 3.8-fold reduction in influenza cases, which is higher than the impact achieved by influenza-specific vaccines. In a separate study focusing on younger populations in Africa, researchers observed a 30% reduction in all-cause mortality and repeated doses of the vaccine produced an additive effect. Other studies have documented OPV's ability to induce protection against bacterial diarrhea, otitis media, genital herpes, and some respiratory pathogens.

Dr. Gallo and colleagues suggest that the OPV vaccine may have similar benefits against COVID-19. An activated innate immune system inhibits viral replication; however, SARS-CoV-2 inhibits innate immune responses. These observations led Dr. Gallo and colleagues to hypothesize that OPV-mediated prolonged interferon activity may be able to counteract SARS-CoV-2's inhibition on the innate immune system. Dr. Gallo noted that other mechanisms of OPV-mediated protection require further study; evidence suggests that epigenetic imprinting through histone methylation may increase the effectiveness of subsequent stimuli and the durability of protection.

Repurposing OPV for Prevention

Dr. Gallo and his team propose to use existing vaccines, specifically OPV, to induce protection immediately in vulnerable populations (e.g., older adults) while COVID-19-specific vaccines and drugs continue to be assessed in clinical trials. Dr. Gallo emphasized that OPV is the best candidate for this strategy because it is inexpensive (approximately 15 cents per dose), readily available, and delivered orally. It also has multiple serotypes, which can be periodically re-administered to induce additive immunity. In addition, OPV is known to protect against other respiratory viruses and is an RNA virus.

OPV has a good safety record, with 1 out of 1 million immunologically-naïve vaccine recipients displaying adverse effects; most of these events are observed in immunocompromised individuals. The risk of adverse effects is minimal in previously-immunized individuals. Circulating vaccine-derived polioviruses emerge only in poorly immunized populations.

OPV Alternatives

Dr. Gallo presented alternative vaccines that could be immediately leveraged and the associated drawbacks for each of them, summarized below:

- The BCG vaccine is injectable, has a poor safety record, results in a permanent scar, and is not scalable.
- The measles, mumps, and rubella (MMR) vaccine is expensive (100X the cost of the OPV vaccine), is injectable, is in low supply, and has significant associated adverse effects.
- The yellow fever vaccine is associated with safety and scalability concerns.

- Live attenuated influenza vaccine has displayed protection against respiratory syncytial virus (RSV) in animal models, but human studies have not been performed.
- Live rotavirus vaccine displays similar advantages to OPV, but remains untested in humans and animal models.
- Live adenovirus vaccine (serotypes 4 and 7) is not licensed for use in the general population and has not been assessed for its ability to induce non-specific protection.

Plan of Action

Dr. Gallo has proposed completing a randomized placebo-controlled clinical trial in medical workers to assess OPV's capacity to prevent COVID-19 directly and controlled human challenge studies against influenza and seasonal coronaviruses to study the mechanism of non-specific protection. The placebo-controlled clinical trial has not yet received funding and may be reformulated to target other populations at high risk of exposure to COVID-19. The human challenge studies could begin soon [for influenza].

Drs. Gallo, Konstantin Chumakov, and Shyam Kottilil have initiated these efforts and are collaborating with multiple institutions (i.e., the University of Maryland-Baltimore's Institute of Human Virology, University of Buffalo, Roswell Park Cancer Center, Cleveland Clinic, and Global Virus Network), as well as Drs. Stanley Plotkin, Stefano Bertozzi, Dean Jamison, Ondrej Mach, Willian Petri, John Modlin, and Lawrence Blatt.

Through these efforts and collaborations, Dr. Gallo aims to provide preventative protection to the general population, to assess OPV as a preventative measure for future waves of influenza and coronaviruses, and to prepare the United States generally for future pandemics.

Discussion

Dr. Nelson Michael noted that discussions to deploy OPV as a preventative measure are ongoing and that he and Dr. Gallo are discussing funding opportunities for the OPV human challenge studies. He added that the United States military provides all incoming recruits with the live adenovirus vaccine (serotypes 4 and 7) and that his team is interested in generating additional data to support the notion that this vaccine could also provide preventative protection.

Dr. Paul Offit expressed surprise that OPV is able to stimulate prolonged interferon activity that is detectable months to 1 year after vaccination. Dr. Gallo noted that the 3.8-fold reduction observed in Russia as a result of OPV deployment against influenza could not have been achieved without prolonged protection; however, researchers did not collect supporting data at the time. The prolonged interferon activity associated with the BCG vaccine is associated with molecular imprinting and histone methylation, leading to protection 1 year post-vaccination; the impact of molecular imprinting and histone methylation on OPV requires further investigation. Because OPV has multiple serotypes, Dr. Gallo is confident that providing multiple OPV serotypes in an additive fashion will allow vaccine recipients to receive protection more than 1 year post-vaccination; however, related data have yet to be collected.

Dr. Offit inquired whether Dr. Gallo knew of other studies investigating alternative non-viral stimulators of interferon activity. Dr. Gallo noted that Dr. Lawrence Blatt is interested in this topic but emphasized that because OPV represents such a safe option, other drugs to stimulate interferon activity may not be needed.

Dr. Doug Lowy inquired whether high-risk populations (e.g., older adults) are likely to experience a strong immune response or an attenuated immune response during the proposed human challenge studies. Drs. Gallo and Chumakov stated that the human challenge studies will not include immunodeficient participants. They cannot predict what type of response high-risk participants would have. The current proposal seeks to assess OPV as a preventative measure; however, a second aim of the studies would be to assess outcomes of participants that are not protected from infection, to see if OPV modifies the severity of disease.

Dr. Paula Annunziato inquired whether OPV's impact on innate immunity suggests that the vaccine can reduce both infection incidence and symptomatic disease incidence and thus whether this information could be used to inform clinical trial enrollment. Dr. Gallo confirmed that OPV reduces both infection and disease incidence.

Dr. Gallo emphasized that vaccines targeting spike proteins may not induce a robust T-cell response and that, if no adverse events or outcomes are observed, the attenuated live virus vaccine being developed in China may be a solution to this pandemic. Dr. Offit inquired whether Dr. Gallo's preference for OPV and attenuated live virus vaccines extends to the vesicular stomatitis virus vaccines, which includes replicating virus. Dr. Gallo responded that he would prefer replicating viral vector vaccines over vaccines using non-replicating vectors. Dr. Chumakov noted that Intravacc is developing a SARS-CoV-2 replicating vaccine that would be delivered mucosally, which may induce both innate and adaptive immune responses.

Dr. Bart Haynes inquired about the potential of the BCG vaccine for a preventive approach and whether a clinical trial with BCG is ongoing. Dr. Gallo noted that the BCG vaccine is costly, leaves participants with permanent scars, and does not have the magnitude of associated data required, compared to OPV. Dr. Chumakov noted that he also prefers OPV compared to the BCG vaccine and that the BCG vaccine induces complications requiring medical attention in 1 out of 100 vaccine recipients; these findings prevent BCG from being suitable for large-scale dissemination, especially for older adults and other vulnerable populations.

Vaccines Clinical Trials Subgroup Discussion

The Vaccines Clinical Trials Subgroup presented the outcomes of the Subgroup's discussion regarding the possibility that a successful SARS-CoV-2 vaccine will be identified and how that finding may impact other ongoing vaccine trials, specifically ongoing trials and trials not yet initiated.

The Subgroup focused on the time period between licensure (or access via EUA) of the first vaccine candidate and identification of correlates of protection or biomarkers. During this time period, the research community must address the ethical considerations of continuing other clinical trials with placebo control, especially in high-risk populations. Dr. Annunziato noted that external data monitoring committees and the public will likely not condone the continuation of other placebo-controlled trials once a vaccine candidate has been approved for licensure and predicted that principal investigators in other efficacy trials may be expected to initiate active-control at least in some sub-populations. Moreover, even without external regulatory pressure, the participants in these ongoing trials may lose some incentive to continue in a trial when another vaccine has been approved. These factors may have significant operational implications for other trials after the first success.

Dr. Annunziato presented the following active-controlled trial considerations:

- What if supply of the licensed vaccine is limited?
- What if a trial of another candidate is expected to reach primary analysis soon?
- What if a vaccine is licensed in some but not all jurisdictions of a multi-national trial?
- What if the licensed vaccine label covers some but not all sub-populations (e.g., only specific age groups)?
- What are the prevalent perspectives about the acceptability of placebo control among participants, providers, regulators, advocates, and researchers?

The Subgroup decided that, in the event that a vaccine becomes available under authorization or approval, the best strategy to support the development of other vaccines is to (1) shorten the time period between licensure and identification of correlates of protection and (2) plan for partial departure of placebo-controlled trials and initiation of active-controlled trials. Shortening the time period will depend on when success is decided upon for the first successful vaccine, which may benefit from alignment on among stakeholders ahead of time, and how much the identification of correlates can be accelerated. Planning for a possible transition from placebo-controlled to active-controlled trials, at least within some sub-populations, will allow the field to examine the considerations involved in continuing a trial (e.g., if it is close to finalizing primary analysis) or discontinuing a trial (e.g., if it has not yet started) and to prepare for anticipated enrollment challenges (e.g., participants depart from a study). It is an open question whether a non-inferiority study against an active control with a clinical endpoint is a feasible possibility.

Discussion

Dr. Lowy inquired whether non-inferiority trials could use a virologic endpoint (e.g., time to clearance) instead of a disease endpoint. Dr. Annunziato noted that this approach could be considered if the active comparator trial had documented impact on the virologic endpoint in question. She also noted that using a virologic endpoint will allow researchers to accrue data more quickly and reduce the required sample size. Whether virological endpoint would be accepted as surrogate endpoints is a question for regulators.

Dr. Jansen inquired whether the actions proposed (i.e., shortening the time period between licensure and identification of correlates of protection and planning for departure from placebo-controlled trials) are hypothetical or will be soon initiated. Dr. Annunziato reported that these considerations are theoretical and general at this time, and not based on individual sponsors' plans or timelines.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*
Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*
Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*
Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*
Marco Cavaleri, PhD, *Head of Biological Health Threats and Vaccines Strategy, European Medicines Agency (EMA)*
Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*
Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*
Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*
Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*
Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Tonya Villafana, PhD, MPH, *Global Medicines Leader, Infectious Diseases, AstraZeneca*

INVITED PARTICIPANTS

Konstantin Chumakov, PhD, *Associate Director of Research, Office of Vaccine Research and Review, CBER, FDA*
Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*
Robert Gallo, MD, *Director, Institute of Human Virology, University of Maryland School of Medicine*
Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*
Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*
Hilary Marston, MD, *Medical Officer/Policy Advisor, NIAID, NIH*
Jackie Miller, MD, *Senior Vice President, Infectious Disease Development, Infectious Diseases, Moderna*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Felicia Qashu, PhD, *Program Officer, Office of Strategic Coordination, NIH*
Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID*
Vivek Schinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*
Stephanie Schrag, DPh, *Epidemiology Team Lead, Division of Bacterial Diseases, National Center*

for Immunization and Respiratory Diseases, CDC

FNIH STAFF

Stacey Adam, PhD, *Science Program Manager, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*

Benjamin Stratton*, Senior Consultant, Deloitte*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Vaccines Working Group (WG) convened to discuss the concern expressed by some members of the vaccine research community and Congress that there could be political pressure to evaluate the safety and efficacy of COVID-19 vaccines prior to the availability of sufficient data from phase 3 trials.

Potential Pressure on Regulators to Evaluate Vaccines without Sufficient Data

Some members of the United States Congress and vaccine researchers in academia have expressed concerns about anticipated pressures on regulators to evaluate a vaccine for use within the United States before the vaccine has met the data requirements laid out in the FDA guidelines. One potential source of pressure is the U.S. presidential election. Another source of pressure is decisions in other countries, such as preliminary vaccine approvals in China and Russia. It is also possible that the AZ/Oxford vaccine could be approved in the UK prior to a decision in the US.

US Congress and the research community have requested that the FDA confirm that they will require phase 3 safety and efficacy data for initial vaccine approvals, and Dr. Stephen Hahn of the FDA has stated in person and in an article that the FDA is committed to this standard. That is reassuring, but not viewed as sufficient to allay concerns about the possible consequences of political pressure. Vaccine developers also share the concern, and have a strong interest in vaccines only being made available after they meet the standards set in the FDA guidelines.

FDA Requirements and Data Generation Timelines

Dr. Kathrin Jansen noted that the FDA has released guidelines regarding the specific requirements and success criteria that must be met before a COVID-19 vaccine is released.

The question of whether it is plausible that the ongoing phase 3 efficacy trials could plausibly generate data that satisfy the FDA guidelines prior to the US elections was discussed. There were different perspectives on the answer to this. Regarding safety, Dr. Larry Corey estimated that at least 20,000 participants will have received two doses of mRNA vaccines by Oct 1 (combined across the Moderna and Pfizer/BioNTech trials). Dr. Jansen noted that typically 3000 participants are required for safety evaluation, a threshold that will be significantly exceeded. The FDA has not provided explicit guidance on COVID-19 vaccine safety requirements, but may require a median follow-up of 2 months for participants (thus earlier-enrolled participants would have 3-4 months of follow-up). Dr. Peter Marks stated that the FDA plans to make clear to everyone within the next week or two what the safety follow-up expectations will be.

Regarding efficacy, the timeline to meet the FDA guidelines depends on the rate of enrollment, the time until endpoints are counted (which begins two weeks after vaccination is complete), the incidence rate of disease, and the efficacy of the vaccine. Some participants expressed skepticism that it was possible that there could be sufficient endpoints by the end of October to meet the efficacy criteria. One vaccine developer expressed the view that it is plausible that there will be sufficient endpoint by then to meet the success criteria, if the vaccine is highly efficacious. In a scenario with a highly efficacious vaccine than can thus meet the success criteria with relatively few endpoints, it was noted that there may not be enough participants from sub-populations to determine if efficacy appears consistent in those sub-populations.

Dr. Michael Santos pointed out that whether a vaccine could generate sufficient data to meet the FDA criteria before the US elections is important: if it were not possible, then blanket statements could be made that any vaccine approval prior to the election was not appropriate. But given the perspective that it is possible that a trial could meet the FDA criteria in October, it is also important not to send the message that any October authorization is inappropriate.

Dr. Marks re-emphasized that the FDA would like a vaccine success as quickly as possible, but this requires appropriate data. He stated confidence that political pressure would not cause FDA staff to support authorization of a vaccine without appropriate safety and efficacy data.

Dr. Ann Arvin noted that when vaccine developers release immunogenicity data it can be confusing to the public that this is different from clinical efficacy. Dr. Marks agreed and emphasized the importance of communicating about the importance of clinical efficacy. Dr. Arvin also noted that communicating about the EUA process will be challenging as well.

Dr. Doug Lowy inquired whether a statement by ACTIV leadership or the Vaccines WG supporting the FDA would beneficial. Dr. Marks suggested that a statement is not needed currently (though would not be objectionable), but that it is possible in the future that there will be a point where additional support may be valuable.

Potential Introduction of Vaccines Approved in Other Jurisdictions

Dr. Jansen asked what the US government could do to introduce a vaccine that had not met FDA standards, including the specific case where a vaccine has been approved already in another country. (b)(5) [redacted]

Dr. Jansen noted that it is possible that a vaccine could be licensed in another country without meeting the requirements set by the FDA. There is precedent for such a vaccine being introduced into the United States: university-based outbreaks of meningitis led the United States government to support introduction of a UK-licensed meningococcal B vaccine under treatment IND (which is a more restrictive mechanism than EUA: treatment IND requires informed consent and the scale was tens of thousands of people rather than potential millions for EUA). This vaccine was eventually licensed in the US without meeting the original criteria that the FDA had established. In this case the foreign licensure was used as partial justification for the introduction of the vaccine, even though the licensure criteria in the UK were not as strict as the FDA had set for the US.

Dr. Tonya Villafana noted that AstraZeneca has a similar approach to other developers: to seek approval with clinical safety and efficacy data. She noted that AstraZeneca has phase 3 trials in the UK, Brazil, and South Africa that have already started and it is possible those studies will read out before US studies. She noted that the upper-age limits have been removed from these studies, so that they do include older participants, but not at the prevalence planned for the US trial.

Dr. Jansen stated the assumption that if these studies produce data that meet the FDA guidelines, there will be no objection to their authorization and approval in the US. Dr. Marks agreed that a decision would depend on the data meeting the criteria, also pointing out that the FDA would like to see data in populations that are representative of the diverse populations of the US.

Dr. Barton Haynes asked what impact an EUA for a vaccine based on data from ex-US trials would have on a US trial of that vaccine; Dr. Marks suggested that there could be justification for continuing the US trial, and that this is a good question for further consideration. Dr. Larry Corey noted that the scenarios for the impact of an EUA on other trials are complicated, depending on many factors. He noted that an ethical review identified the societal benefits of continuing trials, but that participants may not want to continue if a vaccine is available to them outside of the trial setting (without the possibility of receiving a placebo). Dr. Jansen noted that participant discontinuation has been a challenge in oncology trials under analogous circumstances.

Pressure from the Public

Dr. Arvin asked whether there could be public pressure to introduce a vaccine prior to demonstration of clinical safety and efficacy. Dr. Offit noted that, in a recent poll by the Boston Globe, two-thirds of the United States public stated they would accept a COVID-19 vaccine for themselves or their children. Dr. Corey noted that the public expectation is likely for a vaccine to be available around the start of 2021, and are probably not generally aware of the possibility of a vaccine being made available earlier.

Closing

Participants noted that additional discussions are required on this topic in order to prepare for multiple plausible scenarios. Dr. Arvin raised the importance of identification of correlates of protection and the potential challenges to doing so with analyses focused only on antibody responses. Dr. Jansen pointed out that durability of protection will not be established with the initial measures of efficacy. Dr. Corey that vaccines may possibly shift symptomatic disease to asymptomatic infection, and if they do so without significantly reducing transmissibility then introduction of a vaccine under EUA with low coverage may increase the risk for vulnerable populations.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*

Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Susan Buchbinder, MD, *Director of Bridge HIV, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

John Mascola*, MD*, *Director, Vaccine Research Center, NIAID, NIH*

Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Hanneke Schuitemaker, PhD, *Global Health, Viral Vaccine Discovery and Translational Medicine, Johnson & Johnson's Janssen Vaccines*

Jonathan Seals, PhD, *Director, Strategic Science and Technology, Biomedical Advanced Research and Development Authority (BARDA)*

Jim Tartaglia, PhD, *Vice President, Research and Development, Sanofi Pasteur*

Brett Tolman, MA, *Strategy Manager, Deloitte*

Tonya Villafana, PhD, MPH, *Vice President, Global Franchise Head, Infection, AstraZeneca*

INVITED PARTICIPANTS

Kathleen Callahan, MS, *Vice President, Regulatory Affairs, Chemistry, Manufacturing, and Controls, Novavax*

Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*

Ellen Gadbois, PhD, *Program Lead, Biosafety, Biosecurity, and Emerging Biotechnology Policy Division, Office of Science Policy, NIH*

Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*

Markay Hopps, PhD*, Chief of Staff, Vaccine Research and Development, Pfizer*

Hilary Marston, MD, *Medical Officer/Policy Advisor, NIAID, NIH*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Stephanie Schrag, DPh, *Epidemiology Team Lead, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC*
Vivek Schinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*
Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*
Jennifer Verani, MD, MPH, *Epidemic Intelligence Service Officer, Division of Global Health Protection, Center for Global Health, CDC*
Mike Watson, MB ChB, MRCP, AFPM, *President, Infectious Diseases, Moderna*

FNIH STAFF
Stacey Adam, PhD, *Director, Foundation for the NIH (FNIH)*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Vaccines Working Group (WG) invited members of the Coalition for Epidemic Preparedness Innovations (CEPI) who are involved in the Access to COVID-19 Tools (ACT) Accelerator partnership to present their ongoing activities to accelerate vaccine development.

CEPI and the ACT Accelerator Presentation

Overview (presented by Dr. Saville)

CEPI is a private institution that aims to accelerate the development of vaccines against emerging infectious diseases and enable affected populations' equitable access to these vaccines during outbreaks. The current CEPI COVID-19 portfolio includes nine vaccines in development worldwide plus three adjuvant providers; these vaccines work on a variety of platforms (e.g., DNA, RNA, protein, and viral vector) and adjuvant types. CEPI's investment in COVID-19 vaccine development began in January with rapid response platforms and partners that were already engaged with CEPI, and as the pandemic developed expanded to include vaccine platforms with more history of use. Six projects in the vaccine portfolio are currently in clinical trials.

CEPI is a partner within the ACT Accelerator, which is a global collaboration launched to facilitate the acceleration of development, procurement, and equitable access to new COVID-19 diagnostics, therapeutics, and vaccines. The vaccine division of the ACT Accelerator, known as COVAX, includes three subdivisions: (1) development and manufacturing, which is led by CEPI; (2) procurement and scalable delivery, led by Gavi; and (3) policy and allocation, led by the WHO. COVAX's goals are to end the widespread transmission of COVID-19 by developing safe and efficacious vaccines that can be rapidly deployed worldwide and to provide 100M doses of a vaccine for high priority populations in 2020 and 2B doses in 2021. COVAX aims to facilitate collaboration among its partners and with other efforts (such as ACTIV), promote transparency of relevant information and insights, and bear partial responsibility for high risks endured in accelerated development.

SWAT Teams (presented by Dr. Saville)

COVAX's development and manufacturing subdivision includes three SWAT teams (Enabling Sciences, Clinical Development and Operations, and Manufacturing) and a Regulatory Advisory Group (RAG). Each SWAT team provides timely and targeted support to vaccine developers on issues that they identify and connects and coordinates various vaccine organizations to address common challenges together. The RAG acts to support regulatory science questions across all of the SWAT teams. CEPI recognizes other similar efforts, such as those by the NIH and WHO, and wants to avoid duplication while ensuring complementarity such that the entire global perspective is considered for each of the important issues. CEPI is currently soliciting input from vaccine developers on which SWAT team topics are priorities for them, and welcomes input from ACTIV on issues that have been prioritized and where work is ongoing. The SWAT teams oversee task forces as follows:

Enabling Sciences SWAT team (presented by Dr. Kristiansen)

- Assay Standardization task force is developing an international antibody standard in collaboration with the National Institute of Biological Standards and Control (NIBSC), creating centralized testing capabilities to compare vaccine candidates across the same set of assays, defining requirements for diagnostic assay performance, and addressing regulatory challenges related to assay standardization. Currently NIBSC has a research-grade standard panel available, with a goal of progressing to an international standard. The centralized assay capacity will be available to any vaccine developer, not just those funded by CEPI.
- Animal Models task force has established a network to develop animal models, which is available to global researchers, and is assessing published evidence on animal models for safety and efficacy. Goals include providing guidance on vaccine-mediated enhanced disease and correlates of protection.

Discussion

The WG inquired when the international antibody standard would be available to the broader research community. The standard is still waiting for one collection that should come this or next week; it is expected to be distributed for a feasibility study in July. That will be the same material as for the international standard, but it will not have been characterized yet.

Clinical Development and Operations SWAT team (presented by Dr. Cramer)

- The Clinical-operational Readiness task force aims to develop a global clinical trial site network, especially to provide more resources in developing countries, and perform landscape analysis that summarizes vaccine developer participation in different efficacy trial frameworks (Solidarity, ACTIV, etc.).
- The Vaccine Safety task force is developing case definitions for relevant adverse events of special interest (AESIs) and vaccine-mediated enhanced disease. It is also facilitating discussions regarding the balance of speed and safety in accelerated vaccine development and how post-rollout safety surveillance can look for signals of enhanced disease.
- The Clinical Science task force is developing documents summarizing key clinical trial elements (e.g., definitions of endpoints, disease vs. infection, correlates of protection) and is assessing alternative strategies (e.g., human challenge studies) in the event that traditional efficacy trials are not possible. Given that a number of organizations are engaging in this topics, CEPI would welcome engagement in these discussions.

Discussion

Participants asked whether a new safety surveillance system is planned for COVID-19. Dr. Cramer clarified that this effort would leverage existing surveillance systems, recognizing that systems vary across countries and regions and additional effort may be required to analyze data across the world. Dr. Saville noted that this task force is only planning to ensure that there will be good surveillance procedures and will be engaging with other organizations (e.g., the WHO) to implement them.

The WG noted that the current CEPI grantees do not include many developers and manufacturers within developing countries. Dr. Saville noted that CEPI is collaborating with the Developing Countries Vaccine Manufacturers Network (DCVMN) to ensure that these developers are represented within the network. The DCVMN has a representative participating in the discussion of pharmacovigilance.

Manufacturing SWAT team (presented by Dr. Kromann)

- The Drug Product (DP) and Drug Substance (DS) task force is investigating scalable strategies to ensure vaccines can be manufactured for global dissemination and has begun developing a network to give vaccine developers access to manufacturers. This task force has also compiled a list of questions regarding regulatory challenges of DP and DS scalability and shared that with the FDA for review.
- The Supply Chain task force plans to develop strategies by September regarding labelling, raw materials (e.g., vials, stoppers), and quality assurance.
- The Release Assay task force aims to understand potency assay requirements and a support a mutual recognition procedure to allow for timely national releases of vaccine assays. It is collaborating with the European Directorate for the Quality of Medicines and HealthCare (EDQM) and the official medicines control laboratories (OCML) network to assess whether this network has the capacity for these release assays: the testing capacity needs to be aligned to the production capacity.

Discussion

Regulatory agencies have been asked whether in vivo potency release assays will be required for vaccine candidate approval, or if in vitro assays will be sufficient; CEPI's work has focused on the availability of reagents for in vitro assays. Regulators shared that it would be helpful to see proposals from developers and would be happy to take part in cross-cutting discussions. There was some indication from a discussion with EDQM and the OCML network that the perspective may be that in vitro release assays could be sufficient.

The WG inquired about (1) the standardization of clinical assays and harmonization between CEPI and NIH and (2) whether access by vaccine developers to the tools being developed by CEPI requires participation in the access components of COVAX. CEPI has an ongoing collaboration with Dr. Janet Lathey and NIH on establishing centralized laboratory assay capacity and has discussed using the same proficiency panels to ensure harmonization across laboratories. CEPI funding of vaccine development and manufacturing includes requirements for participation in the COVAX fair allocation system. CEPI also provides vaccine developers access to some resources, like centralized laboratories, without specific requirements for access to doses. All manufacturers, funded by CEPI or otherwise, are welcome to participate in the COVAX fair allocation system.

Dr. Santos invited participants to contact him with additional topics for COVAX representatives and the Vaccines WG to discuss. Dr. Saville emphasized the enormity of the shared task and the importance of communication and collaboration to ensure that vaccines are developed rapidly.

Appendix A: Participants List

WORKING GROUP MEMBERS

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*
Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*
Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*
Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*
Marco Cavaleri, PhD, *Head of Biological Health Threats and Vaccines Strategy, European Medicines Agency (EMA)*
Gregory Glen, MD, *President, Research and Development, Novavax*
Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*
Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*
Peter Marks, MD, PhD, *Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*
Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research, U.S. Army Medical Research and Development Command*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*
Hanneke Schuitemaker, PhD, *Global Head, Viral Vaccine Discovery and Translational Medicine, Johnson & Johnson's Janssen Vaccines*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Tal Zaks, MD, PhD, *Chief Medical Officer, Moderna Therapeutics*

INVITED PARTICIPANTS

Svein Rune Andersen, Dr.Sci, *Head of Regulatory Affairs, Europe, Coalition for Epidemic Preparedness Innovations (CEPI)*
Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*
Jakob Cramer, PhD, *Head of Clinical Development, CEPI*
Michelle Culp, BSN, MPH, *Senior Advisor, Office of Science Policy, NIH*
Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*
Holli Hamilton, MD, MPH, *Senior Medical Officer, BARDA*
Paul Kristiansen, PhD, *Head of Standards and Assays, Preclinical and Immunology, CEPI*
Ingrid Kromann, BSc, *Head of Chemistry, Manufacture, and Control (CMC), CEPI*
Nicole Lurie, MD, MSPH, *Strategic Advisor, CEPI*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Oyeronke Oyebanji, MS, *Strategy Coordinator, Vaccine Research and Development, CEPI*
Melanie Saville, MD, *Director of Vaccine Research and Development, CEPI*
Vivek Schinde, MD, MPH, *Vice President, Vaccine Clinical Development, Novavax*

Natalie Thornburg, PhD, *Lead Microbiologist, Respiratory Viruses Branch, CDC*
Jennifer Verani, MD, MPH, *Epidemic Intelligence Service Officer, Division of Global Health Protection, Center for Global Health, CDC*
Debra Yesky, PharmD, *Head of Regulatory Affairs, North America, CEPI*
John Young, PhD, *Global Head, Infectious Diseases, Roche*

FNIH STAFF
Stephanie James, PhD, *Senior VP of Science, Foundation for the NIH (FNIH)*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Jonathan Wachtel, MBA, *Manager, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Vaccines Working Group (WG) discussed two new aspects of its remit: (1) to write a perspective on the scientific and practical considerations for a COVID-19 human challenge model and (2) to support the development and launch of a harmonized master protocol trial. They also discussed possible pathways to vaccine approval/authorization to pursue in parallel with a full development pathway including a phase 3 trial and traditional approval; the Protective Immune Responses Sub-Group will discuss identifying the datasets required to support pursuing these pathways during the next Sub-Group meeting.

ACTIV is developing an external communications strategy that will publicize efforts of the ACTIV partnership biweekly; more details will be forthcoming.

New Mandates for the Vaccines WG

Dr. Francis Collins charged the Vaccines WG with two new mandates: (1) to write a perspective on the scientific and practical considerations for a COVID-19 human challenge model, to be completed by May 15, and (2) to support the development and launch of a harmonized master protocol for an adaptive phase 2/3 trial, to be ready for implementation by July 1.

Drs. Cohen, Corey, Marovich, Michael, Neuzil, Offit, and Robb have volunteered to draft the human challenge model manuscript. This manuscript will complement existing treatments of the topic, which have primarily focused on ethics, such as a bioethical consultation from Dr. Christine Grady. The topic will be presented during the May 11 Vaccines WG meeting.

Dr. Mascola and his colleagues at NIAID are drafting a protocol for the adaptive phase 2/3 trial, which will be shared with the WG for further refinement. The primary locus of this work will be the newly formed Vaccines Clinical Trials Sub-Group. Working Group members are invited to participate in that Sub-Group or recommend participation by others.

Alternative Pathways to Vaccine Approval

The Protective Immune Responses Sub-Group has discussed the possible pathways to vaccine approval/authorization that could be pursued in parallel with a full development pathway including a phase 3 trial and traditional approval. They compiled a list of possible sources of evidence that in some combination may suggest vaccine efficacy, such as:

- Antibody levels associated with post-infection immunity
- Data from studies of convalescent plasma and specific immune globulins
- Efficacy signals from larger Phase II trials
- Animal challenge models
- Data from population-based vaccine studies

If evidence from these sources can provide a biomarker that is reasonably likely to predict protection, it may be possible for a vaccine candidate to receive accelerated approval. This is important because the epidemiology is uncertain, as is the threshold for sufficient efficacy, and it may take longer than we anticipate to accumulate enough efficacy events to meet the threshold. In that case we could have thousands of safety endpoints but insufficient efficacy endpoints, and an accelerated approval path could be very important.

Participants discussed the challenges and opportunities of identifying correlates of protection. It was noted that many licensed vaccines still do not have immunological correlates of protection. There are hypotheses about that nature of what could constitute a protective response for CoV2, such as neutralizing antibodies, but this is still a hypothesis (anecdotal reports of possible reinfection do not seem compelling enough to cast doubt on this hypothesis). The search for correlates is a standard component of vaccine development to enable product lifecycle management. The current collaborative environment may present a new kind of opportunity: the vaccines that are furthest along may generate data on correlates that can be shared openly, enabling better decisions about other candidates in development to more efficiently advance to the goal of having multiple vaccines available for use globally. If a mechanistic correlate of protection is identified during the development of a vaccine, regulators can consider that correlate in decisions about other vaccine candidates, including the potential for traditional approval if the correlate is scientifically well established.

Participants discussed that there can be two dimensions to vaccine efficacy: protection of an individual from severe disease, and prevention of transmission from an infected individual. The hope is that a vaccine would be able to provide both forms of efficacy. [Comment from Mike Santos: This question seems interesting to contemplate. If most of the transmission is coming from low/no-symptom URI, then in principle perhaps a vaccine could protect against LRI and severe disease without protecting against the high-transmission URI phase. In practice perhaps that is unlikely for antibody-mediated protection. The converse would perhaps be a vaccine that only protected in individuals with strong immune responses, protecting the younger and healthier from infection and thus reducing transmission, but didn't protect elderly populations from infection and disease. Hopefully also unlikely.] There is also the possibility of prevention of infection, though the challenge of definition of infection and sufficiently sensitive assays was raised (this was a challenge when considering such approaches for Zika virus). TPPs could be developed for each of these dimensions, and prevention of infection was suggested as an endpoint to be considered for approval/authorization decisions.

Currently regulators have been focused on the data packages required for FIH studies, but have begun to receive proposals for efficacy studies. Primary endpoints being looked at now are clinical disease with virologic confirmation. Asymptomatic infection is also being looked at as secondary endpoint. It has not yet been considered that different vaccines could have different primary endpoints for different TPPs. There also is not a specific perspective on exactly what stage or markers of clinical disease. Participants also separately discussed what surrogates for clinical outcomes would be considered (in analogy to CIN2+ as a surrogate for cervical cancer in HPV vaccine development), given that a mortality endpoint is not practical.

As COVID-19 treatment evolves, the ability to evaluate disease endpoints in a vaccine trial may change. As an example, convalescent plasma or other treatments administered upon hospital admission may change the disease course and reduce severe disease incidence. In some cases vaccine clinical trial participants may not have access to the highest levels of care, which may mitigate this. Questions of equipoise and appropriate standards of care are common in prevention trials, and there is experience dealing with them.

Dr. Arvin noted that natural history studies focusing on household exposures may provide insight into protective correlates. Studies are quickly getting started, but how soon these data are available is still a question.

Dr. Watson also suggested consideration of progressive endpoints in the context of the clinical trial protocol development, such as looking at prevention of infection, prevention of disease, and prevention of severe disease. This takes advantage of the relatively larger numbers of infection than disease endpoints, and disease than severe disease endpoints, recognizing that this requires alpha spend for the looks at the earlier endpoints. It would be interesting to see a statistical analysis of the implications for trial size.

Dr. Jansen noted that an important method to accelerate progress in vaccine evaluation may be to develop a data package (including some of the data types listed above) that provides evidence for vaccine efficacy. The next steps for the Protective Immune Responses Sub-Group are to develop a plan to generate this data package while continuing to pursue the path to phase 3 efficacy trials and traditional approval.

Dr. Santos noted that ACTIV leadership includes members of the European Medicines Agency (EMA) and invited members of the Vaccines WG to contact him if they feel that EMA participation within this WG would be beneficial.

ACTIV External Communications Approach

The ACTIV partnership will begin to provide communications and updates to the public regarding ACTIV efforts. These communications will be released biweekly following ACTIV leadership meetings. The exact mechanism for developing talking points for these releases and the ways ACTIV WGs can contribute are still being developed, but Dr. Santos will provide that information when it becomes available.

Next Steps

Dr. Michael will share the current human challenge study considerations manuscript, the bioethical consultation from Dr. Grady, and the recent human challenge studies paper from JID with Dr. Santos, who will circulate these documents to the Vaccines WG for feedback.

Vaccines WG members will discuss the human challenge study manuscript during the next WG meeting.

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WORKING GROUP MEMBER PARTICIPANTS

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Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Beth Bell, MD, MPH, *Former Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC, and Clinical Professor, University of Washington*

Susan Buchbinder, MD, *Director of HIV Prevention Research, San Francisco Department of Public Health, and Professor, UCSF*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*

Mark Davis, PhD, *Director, Institute for Immunology, Transplantation and Infection, Stanford University*

Emmanuel Hanon, PhD, *Senior Vice President of Vaccines Research and Development, GSK*

Barton Haynes, MD, *Director, Human Vaccine Institute, Duke University School of Medicine*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of Medicine, and Director, Texas Children's Center for Vaccine Development*

Antonio Lanzavecchia, MD, *Director, Immune Regulation, Institute for Research in Biomedicine*

Nelson Michael, MD, PhD, *Director, Center for Infectious Disease Research, Walter Reed Army Institute of Research*

Nancy Messonnier, MD, *Director, National Center for Immunization and Respiratory Diseases (NCIRD), Centers for Disease Control and Prevention (CDC)*

Paul Offit, MD, *Professor, University of Pennsylvania, and Director, Vaccine Education Center, Children's Hospital of Philadelphia*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

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Jim Tartaglia, PhD, *Vice President, Research and Development, Sanofi Pasteur*

Brett Tolman, MA, *Strategy Manager, Deloitte*

INVITED PARTICIPANTS

Myron Cohen, MD, *Director for Global Health & Infectious Diseases, University of North Carolina School of Medicine*

Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*

Peter Gilbert, PhD, *Biostatistician, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center*

Marion Gruber, PhD, *Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)*

Markay Hopps, PhD*, Chief of Staff, Vaccine Research and Development, Pfizer*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Julie Ledgerwood, DO, *Senior Clinician, Vaccine Research Center, NIAID*

Mary Marovich, MD, *Director, Vaccine Research Program, NIAID*

Hilary Marston, MD, *Medical Officer/Policy Advisor, NIAID, NIH*

Kayvon Modjarrad, MD, PhD, *Direction, Emerging Infectious Diseases, Walter Reed Army Institute of Research*

Kathy Neuzil, MD, MPH, FIDSA, *Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Felicia Qashu, PhD, *Program Officer, Office of Strategic Coordination, NIH*

Merlin Robb, MD, *Chief Medical Advisor, Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.*

Mike Watson, MB ChB, MRCP, AFPM, *President, Infectious Diseases, Moderna*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

FNIH STAFF

Stacey Adam, PhD, *Science Program Manager, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science, FNIH*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Karen Tountas, PhD, *Scientific Program Manager, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Margaret Anderson, MA, *Managing Director, Deloitte*

Bethany Stokes, MS*, Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

Representatives of all ACTIV trial teams convened to receive trial status updates and discuss issues and best practices. Participants reviewed ongoing initiatives to engage the healthcare provider community in implementation of therapeutics, reviewed the HHS portal designed to centralize provider and patient engagement, and heard a summary of the most recent ACTIV Leadership Team meeting, at which the Vaccines WG presented a new plan to test vaccine impact on virus transmission. Participants also raised the issue of EUA implications for clinical trials and recommended further discussion of that challenge.

Action Items

- Trial team members will be contacted by Dr. Stacey Adam for assistance in assembling a master site list for all ACTIV trials

Trial Status Updates

ACTIV-1

ACTIV-1 has opened 14 sites and (b) (4) . More than fifty sites have been engaged in the U.S. and an additional 20 have been identified in Latin America. The trial team is revising its protocol to simplify and clarify several elements, including co-enrollment with ACTIV-4.

ACTIV-2

ACTIV-2 has opened 69 sites and (b) (4) 4 of them in the Phase II trial of the (b) (4) neutralizing antibody (nAb). Enrollment is currently paused as ACTIV-2 transitions from that now-completed phase II study to the opening of an open-label phase III study of the same agent (the transition will occur upon IRB approval of the LOA and distribution of phase III laboratory kits, both of which should be complete by November 23). ACTIV-2 is also developing Version 2 of its protocol, which will test a (b) (4) . Version 2 will be submitted to FDA by November 23. Several non-infusion agents are planned for Versions 3 and 4.

The EUA for (b) (4) agent has raised several ethical questions for ACTIV-2. First, the treatment authorization has raised doubts among some clinicians about the appropriateness of continuing a placebo-controlled trial. ACTIV-2 has solicited a formal ethics consultation on this question, but initial guidance from its DSMB—reinforced by public guidance from the Guidelines Committees of the Infectious Diseases Society of America (IDSA) and HHS—has emphasized that (b) (4) agent is not the standard of care and has thus argued strongly against a change in trial design. Second, the distribution of (b) (4) agent through a narrow set of large institutions may exacerbate concerns that clinical trial infrastructure is not designed to serve the populations at greatest risk of COVID-19. ACTIV-2 is considering how to build equitable distribution models that prioritize these populations and defuse this concern. The EUA may also have practical effects on infusion capacity and enrollment, as institutions seek to incorporate an income-generating treatment and patients seek what they perceive to be an approved therapy.

ACTIV-3

ACTIV-3 has completed its trial of Lilly's nAb and has prepared a manuscript analyzing the results that is currently under review by the *New England Journal of Medicine.* Fifty-one sites were registered for Version 1 of the protocol and will re-open with agents from Brii Bio and GSK-Vir when Version 2 is approved. FDA comments on Version 2 recommended one primary change: the extension of patient follow-up to 18 months post-90-day endpoint, based on the long half-life of tested agents. The trial team is incorporating this change and finalizing the revised protocol for regulatory review at NIAID, the central IRB, and then ex-U.S. regulatory authorities. (Version 2 will also allow co-enrollment with other trials.) ACTIV-3 has already begun preparing Version 3, which will be submitted to FDA after AstraZeneca submits its Phase I study results on December 14. Additional agents are under consideration.

ACTIV-4

ACTIV-4A has activated 16 sites and (b)(4) [redacted] The trial team has developed two new arms to test (1) a P2Y12 inhibitor plus prophylactic-dose anticoagulant and (2) a P2Y12 inhibitor plus therapeutic-dose anticoagulant; this plan was submitted last week to the CONNECTS Steering Committee for initial review. ACTIV-4 has also now incorporated the PROTECT trial, which is part of a multiplatform RCT collaboration (along with REMAP-CAP and ITAC) with approximately 1,000 total patients; DSMB review is expected within the next several weeks. ACTIV-4A is ready to begin co-enrollment with ACTIV-1 and -3 once those trials have completed their protocol revisions.

ACTIV-4B has opened 4 sites and (b)(4) [redacted]. The trial team has begun working with a new CRO that is expected to streamline contract negotiations and thus accelerate site activation and enrollment. ACTIV-4B is also interested in co-enrollment with ACTIV-1 and -3 when it becomes available.

ACTIV-4C has completed trial documentation and is awaiting final approval from regulatory bodies. The trial team has secured Covance as its CRO and has identified an initial seven networks for potential site activation.

ACTIV-5

ACTIV-5 will soon have 7 open sites and has (b)(4) [redacted]. The trial team is assessing several new investigational agents.

Provider Community Engagement

Kevin Bugin, PhD

As potential treatments against COVID-19 continue to be identified, ACTIV has begun to focus on how to promote their implementation. Study teams have identified two broad challenges that can hinder use of available therapeutics: (1) lack of provider awareness and (2) existence of various local barriers. Dr. Kevin Bugin described how various initiatives developed to support clinical trials may help overcome both of these challenges.

Increase Provider Awareness

Many providers may not be aware of the broad portfolio of options to treat COVID-19 across the patient lifecycle. Existing study team efforts to connect providers and the public to ACTIV trials should help improve awareness. For example, by recently engaging larger Integrated Delivery Networks (IDNs) in ACTIV trials, study teams may increase the number of providers—and patients—who are familiar with therapeutics currently being tested. Ongoing cross-trial marketing can help promote appreciation of the diversity of treatments that are relevant to COVID-19 patients, from antivirals to symptomatic therapies. This external marketing will soon be supported by the launch of the hhs.gov/combatcovid portal, which will help educate patients and providers about already available therapies as well as trials.

Address Local Barriers

Even providers who are aware of therapeutics may face local logistical challenges to delivering them. The multi-faceted logistical support ACTIV is delivering to clinical trial sites should also help address treatment barriers. ACTIV has supported the expansion of clinical infrastructure (especially infusion capacity), augmentation of site staffing and training, and development of patient-facing resources (such as flip books), all of which should equip providers to better deliver treatments to patients. Similarly, its assistance to sites navigating trial competition has helped streamline logistical challenges that would otherwise have obstructed therapeutic delivery. Participants suggested that the integration of mobile phlebotomy units into trial sites would be another way to improve trial and site capacity.

Implications of EUAs

While ACTIV aims to support the implementation of evidence-based therapeutics, it must also develop plans to ensure that studies can continue to collect evidence as more EUAs are granted. Providers and patients may misconstrue EUAs as approvals of efficacious agents rather than authorization of agents that are *not* yet proven to help but that are unlikely to harm. This misreading leads providers and patients to seek perceived therapeutics over studies of them.

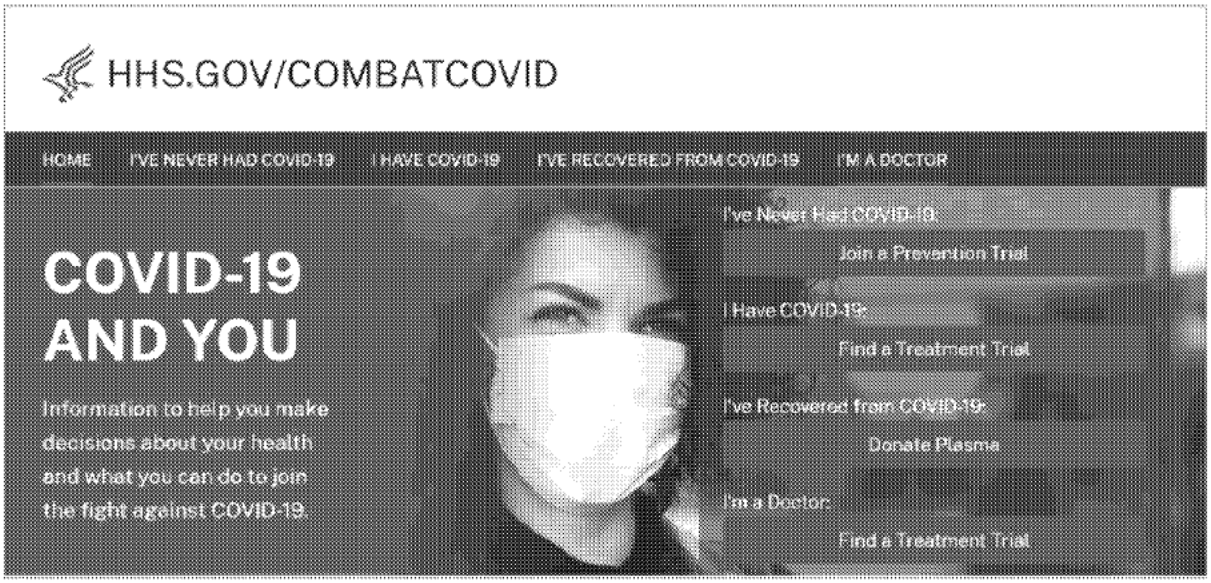
Lilly's nAb has increased pressure to develop EUA-related plans. Dr. Peter Kim reported that hospital administrators at several ACTIV-2 sites have expressed an interest in taking infusion space built for clinical trials and repurposing it for implementation of the Lilly EUA. Dr. Bill Powderly suggested that these requests demonstrate both the near-term security and the long-term vulnerability of ACTIV trial recruitment: many healthcare systems simply cannot afford to scale up administration of the Lilly nAb in the near term, but a future agent with a similar apparent efficacy profile and easier administration would sap clinicians' will to refer patients to any trial. Dr. Judy Hochman noted that this problem is also illustrated by convalescent plasma: the EUA for plasma has put in widespread use an agent that to date shows no benefit in placebo-controlled trials and it may actually undermine enrollment in those trials.

Messaging plays a role in ameliorating or exacerbating misconceptions of EUAs. Dr. Powderly noted that some providers may currently be describing ACTIV-2 as a way to deliver the Lilly nAb, which reinforces the misperception that clinical trials are completed when EUAs are granted. He suggested that this messaging can be hard to control: the fact that ACTIV-2 is not currently randomizing patients may be misperceived as an embrace of an EUA-approved agent. (Dr. Kim noted that the IDSA approached ACTIV-2 out of concern that the trial was simply delivering Lilly's nAb; in reality, the fact that Lilly will not commercialize the agent precluded further placebo-controlled study.) Manufacturers also contribute to misperceptions of EUAs by seeking them over approvals; one company participating in ACTIV-2, for example, asked the trial team how much data it needed to obtain an EUA, as if that were the point of ACTIV.

These challenges may be somewhat specific to the United States: Dr. Jens Lundgren noted that no ex-U.S. regulatory authority has considered emergency release of the Lilly agent, based on the thinness of evidence supporting it and the need to complete placebo-controlled trials.

HHS.GOV COVID PORTAL

The hhs.gov/combatcovid portal, which acts as a landing page for all federally-supported COVID-19-related efforts, will have a soft launch on November 24 and a formal launch by November 30. The portal sorts visitors into four pathways (pictured in the graphic below) that link to information about prevention trials (including CoVPN's prophylactic Ab trials as well as vaccine trials); convalescence (including plasma donation and referrals to ACTIV-4C when that protocol launches); treatment options for physicians (including NIH treatment guidelines and list of clinical trials); and treatment trials for newly-diagnosed individuals (including descriptions of—and where relevant links to—ACTIV, C3PO, ACTT, CONTAIN COVID-19, ITAC, and PASSITONI, as well as a referral to the ACTIV and ACTIV-associated trial call center).



Information to help you make decisions about your health and what you can do to join the fight against COVID-19.

Leadership Team Meeting Update

At its November 19 meeting, the ACTIV Leadership Team recognized the tremendous work of all ACTIV participants and reiterated its readiness to provide any additional support for participants' efforts. The leadership also announced that it recently revived ACTIV's Vaccines WG, after a 3-month hiatus, with the charge to evaluate potential implications of a vaccine EUA. The Vaccines WG is currently considering four main topics: (1) impact of efficacious vaccines on virus transmission, (2) potential blinded cross-over for ongoing phase III trials post-vaccine introduction, (3) preparations for the possibility that vaccine efficacy will vary by platform and product, and (4) evaluation of vaccines in immunocompromised populations. The WG has also begun planning several trials to address vaccine impact on transmission.

The ACTIV Trial Oversight Committee has called for a parallel effort to consider how vaccine authorizations may require new kinds of therapeutic trials, including trials to assess the potential impact of nAb treatment on subsequent vaccination response. Dr. Sarah Read noted that NIAID's Prevention Group has been discussing ways to explore this question and urged that any ACTIV sub-study coordinate with its efforts. Participants suggested that ACTIV might also study breakthrough infections in vaccinated individuals or risk of reinfection. These efforts could benefit from cross-trial data-sharing to enable prospective tracing of patients.

To support the increasing complexity of the ACTIV trial landscape, a master site list is being developed to map potential co-enrollment opportunities, avoid trial competition, and assist (b) (4) in identifying new sites that are not already known to ACTIV. Some trial teams have already contributed to the list's creation and others will be contacted by Dr. Adam for information.

Appendix A: Participants List

TRIAL TEAM MEMBERS

ACTIV-1

William G. Powderly, MD, *ACTIV-1 Chair and J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Sam Bozzette, MD, PhD, (not in attendance) *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Lisa LaVange, PhD, (not in attendance) *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

ACTIV-2

David (Davey) Smith, MD, (not in attendance) *ACTIV-2 Chair Professor of Medicine, U. California, San Diego*

Judith Currier, MD, (not in attendance) *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Michael Hughes, PhD, (not in attendance) *Professor, Department of Biostatistics, Harvard University*

Cyrus Javan, MD, MPH, *Medical Officer/Program Officer, Division of AIDS, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

ACTIV-3

James D. Neaton, PhD, *ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen*

Birgit Grund, PhD, *Associate Professor of Statistics, University of Minnesota*

Laura McNay, MS, *Deputy Director for Operations and Management, Director, Office of Planning and Operations, NIAID/NIH*

ACTIV-4

Judith S. Hochman, MD, *ACTIV-4A Chair and Harold Snyder Family Professor of Cardiology, Department of Medicine, NYU Grossman School of Medicine*

Paul Ridker, MD, (not in attendance) *ACTIV-4B Chair; Senior Physician, Brigham and Women's Hospital; Eugene Braunwald Professor of Medicine, Harvard Medical School*

Tom Ortel, MD, PhD, *ACTIV-4C Chair and Chief, Division of Hematology, Department of Medicine, Duke University*

Scott Berry, PhD, *Adjunct Professor, Department of Biostatistics & Data Science, Kansas University Medical Center*

Jean Connors, MD, *Associate Professor, Department of Medicine Brigham and Women's Hospital*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI, NIH*

Eric Leifer, PhD, *Mathematical Statistician, NHLBI, NIH*

Allison Morris, MD, *ACTIV-4D Co-Chair and Professor of Medicine, Immunology, and Clinical and Translational Research, University of Pittsburgh*

Frank C. Sciurba, MD, (not in attendance) *Professor, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh*

Abdus Wahed, PhD, (not in attendance) *Professor, Department of Biostatistics, University of Pittsburgh*

Clinton B. Wright, MD, *Director, Division of Clinical Research, National Institute of Neurological Diseases and Stroke (NINDS), NIH*

ACTIV-5

John Beigel, PhD, (not in attendance) *Division of Microbiology and Infectious Diseases, NIAID, NIH*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases*

OPERATION WARP SPEED

Tom Stock, DO, *Clinical Advisor to ACTIV-1 and Former Vice President, Clinical Development and Operations, Pfizer*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, (not in attendance) *Clinical Advisor to ACTIV-3 and Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

David Douglas, *Clinical Advisor to ACTIV-4 and Former Head, Global Research and Development Project Management Office, Pfizer*

Ciaran Lawlor, PhD, (not in attendance) *OWS Consultant, Boston Consulting Group*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Sheri Parker, PMP, PhD, *CAPT, MSC, USN, Therapeutics Clinical Operations Director, Operation Warp Speed*

Ritika Philip, (not in attendance) *OWS Consultant, Boston Consulting Group*

Col. Deydre Teyhen, *DPT, PhD*, *Director of Therapeutics, Operation Warp Speed*

TX-CLINICAL WORKING GROUP

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-Chair)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*
Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, *Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)*
Krishna Deepak, MS, *Consultant, Boston Consulting Group*
Nancy Geller, PhD, *Director, NHLBI Office of Biostatistics Research, NIH*
Raahul Ramakrishnan, MD, *Project Leader, Boston Consulting Group*
Nada Saleh, MS, (not in attendance) *Clinical Trials Specialist, Social and Scientific Systems*
Austin Van Grack, MS, *Committee Coordinator, Social and Scientific Systems*

STAFF

Evan Appell, *Consultant, Deloitte*
Alex Sorosa, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received brief updates on ACTIV-2 and ACTIV-3 trials and discussed other topics escalated for its consideration, including an issue prompting study pause and full data review of ACTIV-3 by the Data and Safety Monitoring Board (DSMB), manufacturing issues with (b) (4)), and opportunities to increase enrollment for ACTIV-2. In response to the DSMB's request for study pause and data review, the TOC discussed implications for the ACTIV-3 trial amendment and new agent onboarding, including the potential to consider evaluating other classes of agents in ACTIV-3.

Trial Accrual and Status Updates

The TOC received brief status updates on ACTIV-2 and ACTIV-3 accruals and timelines.

ACTIV-2

ACTIV-2 has opened 36 sites and (b) (4) . Although (b) (4) s Emergency Use Authorization (EUA) request is still pending, ACTIV-2 sites have begun converting from the (b) (4) to (b) (4) drug.

ACTIV-3

ACTIV-3 had opened 49 sites and (b) (4) prior to being put on hold. The ACTIV-3 team has been very successful at activating sites, with a large uptick in enrollment during the most recent 5 days. It is unclear what effect the trial's pause will have on site activation and enrollment.

Discussion

The ACTIV-2 trial team reported 34 of the 36 open sites have switched to the (b) (4) drug. The trial team is currently preparing a letter to the FDA seeking to streamline ACTIV-2 protocols.

The ACTIV-3 trial team reiterated the need to communicate with companies interested in the ACTIV-3 trial about new agent onboarding and agent prioritization.

Topics for Discussion

ACTIV-3 Trial Halted Pending DSMB Review

ACTIV's baseline DSMB activities include protocol-based evaluations of interim data as well as the evaluation of any adverse events (AEs) reported by study sites. One of the protocol-specified checkpoints was triggered when enrollment passed 300 participants, prompting an interim review of ACTIV-3 study data by the DSMB scheduled for October 26. However, after a regular weekly unblinded review of AEs, the DSMB alerted the ACTIV-3 trial team that a protocol boundary had been crossed. The DSMB recommended the October 26 meeting be used to conduct a full review of day 5 ordinal outcomes for all (b) (4) currently enrolled in ACTIV-3. Out of an abundance of caution, the DSMB also recommended that enrollment in ACTIV-3 be halted until the full data are reviewed. The DSMB stated that their concerns with the ACTIV-3 trial do not extend to ACTIV-2, and they will provide written documentation of this limitation to ACTIV.

Dr. (b) (6) explained the day 5 outcomes for ACTIV-3 include a pulmonary complications outcome, similar to the ACTT protocol, as well as an "other organ failure" outcome; both outcomes are assessed with the same boundaries. While the DSMB has not revealed which boundary was crossed, the ACTIV-3 trial team considered it likely that the boundary related to harm. Dr. (b) (6) offered two possible explanations: (1) an issue with protocol design (e.g., day 5 ordinal comparison does not track with long-term outcomes) or (2) a safety signal associated with the administration of large quantities of monoclonal antibodies (mAbs).

The ACTIV-3 trial team has contacted site protocol teams and data are being prepared for the DSMB review. (b) (4) has expressed interest in seeing these data and the DSMB is considering sharing them with a select group of firewalled individuals at the company. The trial team is waiting for a response from FDA on whether they will require any additional documentation prior to the DSMB review.

Implications for ACTIV-3 Trial Amendment and New Agent Onboarding

In addition to halting enrollment, the DSMB asked that submission of the ACTIV-3 trial amendment and any new appendices for regulatory approval be held pending the outcome of the October 26 meeting. Prior to this request, the ACTIV-3 trial team had intended to submit one protocol amendment to FDA that would address changes to Phase III, Stage 2, and simultaneously bring in agents from (b) (4), with the assumption that (b) (4) would advance to stage 2.

Because the protocol amendment cannot be submitted until after October 26, some TOC members felt that it would be beneficial to revise it to include (b) (4) agent together with the agents from (b) (4). The prospect of simultaneously onboarding the three agents is attractive because it avoids the submission of an additional amendment and brings agents on at a moment when enrollment is accelerating. However, other TOC members noted that this approach risks delaying the onboarding of the other two agents, because it is not yet clear that (b) (4) will be ready to proceed with ACTIV by October 26. Such a risk seems particularly unreasonable because (b) (4) has caused the delays by continuing to renegotiate terms with ACTIV.

The TOC agreed to move forward with the protocol amendment that includes appendices for (b) (4), provided the DSMB does not indicate there is a class effect. Dr. (b) (6) will respond to (b) (4) on the TOC's behalf, but the TOC will not wait for (b) (4) reply before submitting the protocol amendment to FDA.

Regarding (b) (4) the TOC agreed to share a draft of the revised protocol with (b) (4) and to address their other question. In addition, the reply to (b) (4) will once again request that the ACTIV DSMB be permitted to review (b) (4)'s safety data. Although (b) (4) previously refused to share data from their study, TOC members noted that their objection seemed related to the request for efficacy data. If the issue raised by the ACTIV-3 DSMB is a real safety signal, then safety data for (b) (4) agent may be important. To complete an appendix for (b) (4) the ACTIV-3 trial team recommended that three to four calls be scheduled.

The TOC will also update (b) (4) the status of the ACTIV-3 trial and the intent to submit appendices for their agents to FDA on October 26, unless the DSMB identifies a class issue with mAbs.

Explore Other Classes of Agents for ACTIV-3

The ACTIV-3 trial team felt it may be beneficial to formulate a proactive strategic plan to address potential outcomes of the DSMB review meeting. The TOC agreed and noted that the key question is whether the issue raised by the DSMB is a real safety signal, in which case it is likely to be a class effect. If the DSMB review rules out a class effect, then ACTIV-3 will continue to focus on the agents already in the pipeline. If the DSMB cannot determine whether a class effect exists, then ACTIV-3 should be prepared to pivot the existing infrastructure of study sites to a new class of agents.

Dr. (b) (6) indicated that the Agent Prioritization Committee (APC) has other agents in its queue, including the (b) (4) and injectable antivirals. She added that the APC can allow trial managers to join their committee; trial members are recused from some votes, but their subject matter expertise is appreciated. Dr. (b) (6) offered to assemble a list of potential agents and to set up a meeting between the APC and ACTIV-3 team leads. In addition to agents in the APC queue, Dr. (b) (6) noted that DARPins may also be candidate agents, with one from (b) (4) currently under review by the Agent Selection Committee (ASC). While (b) (4)' early animal data were not compelling, (b) (4) and USG labs are in the process of generating independent data for the agent. Dr. (b) (6) will follow up with (b) (4) on the status of their discussions with FDA.

Dr. (b) (6) offered to share the Operation Warp Speed (OWS) watchlist.

(b) (4)

A regulatory issue with one of (b) (4) sites used to produce their (b) (4) became public this week. TOC members discussed any potential implications of this news for the ACTIV-2/-3 trials. Dr. (b) (6) advised the TOC that the FDA has been aware of this issue for almost a year. Any information other than the FDA Form 483 and warning letters is proprietary. ACTIV can request additional information from the FDA, but Dr. (b) (6) advised that FDA is unlikely to respond to such a request. She recommended that the TOC trust that the FDA will disclose any issues that might affect the ACTIV trials. In addition, (b) (4) would be responsible for disclosing any problems that would prevent the company from moving forward with ACTIV. The TOC agreed no action was needed at this time.

Opportunities to Increase ACTIV-2 Enrollment

Dr. (b) (6) met with Drs. (b) (6) to discuss opportunities to increase enrollment in ACTIV-2. They identified two potential avenues:

Identification and Recruitment of Additional Sites

Dr. (b)(6) is seeking National Cancer Institute (NCI) permission to leverage their NCORP sites – a network of 45 sites in underrepresented communities – to expand the ACTIV network. NCORP sites would open access to the Midwest, while current ACTIV-2 sites are clustered largely on the coasts. However, even if ACTIV secures NCI's permission to contact NCORP sites, it is possible they will not consent to participate due to concerns that their patient population is high risk for COVID-19. Dr. (b)(6) is also approaching other NIH Institutes and Centers (ICs) to identify other networks across NIH that ACTIV may be able to leverage.

Dr (b)(6) offered OWS funding and materiel resources to support these efforts.

Leverage Government and Industry Resources for Site Activation and Enrollment

Recent surveys of the ACTIV clinical sites highlight a need for additional resources, especially at high-performing sites. In addition, site activation remains an issue.

Dr. (b)(6) suggested enlisting clinical operations teams from industry to support open ACTIV sites, and Dr. (b)(6) noted OWS is working on mobilizing government teams to assist with site activation. ACTIV trial teams welcomed these offers of assistance. Even if the legalities of these arrangements can be managed, however, the TOC recognized that an additional component to the success of this strategy is integration of these teams into the CRO's processes. They considered that ACTIV may need to enlist an additional CRO to help achieve this goal.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota and Principal Investigator, INSIGHT*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Erica Ollmann Saphire, PhD, *Professor, La Jolla Institute for Immunology*

David (Davey) Smith, MD, *Professor of Medicine, U. California, San Diego*

Janet Woodcock, MD, *Therapeutics Lead, Operation Warp Speed*

OTHER INVITED ATTENDEES

Elizabeth Church, PhD, *Deputy Director, Therapeutics Research Program, Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), NIH*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*

Helen Q. Chen, *Consultant, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

David Goff: **00:28:12**

Supportive of the proposed plan.

davey: **00:51:43**

some hospitals may not want inhaled or nebulized agents because of infection control issues. just FYI

Stacey Adam: **00:51:57**

Thanks, Davey!

Bill Erhardt: **00:52:24**

Do you know if (b) (4) can be administered via neb or does it have to be through their proprietary device?

davey: **00:52:49**

just their device

Stacey Adam: **00:52:52**

Not sure. Can ask them.

Bill Erhardt: **00:53:04**

If device only, that could be difficult that could be difficult for people with respiratory compromise.

davey: **00:53:17**

my hosp infection control person did not like it...

davey: **00:53:26**

agreed

Janet.Woodcock: **00:53:46**

Right that is a big problem for inpatient use.... jw

David Goff: **01:04:33**

primary care practice-based networks?

Stacey Adam: **01:04:48**

nope mainly cancer

ACTIV Trial Oversight Committee

Ad Hoc Meeting with ACTIV-2 Leadership, Meeting Minutes

Wednesday, November 25th, 2020

Action Items

Action Items		
	Information	**POC**
1	Schedule a meeting between major trial networks to discuss lead for (b) (4)	(b) (6)
2	Visit combatcovid.hhs.gov and alert the TOC or (b) (6) of any issues	**All**

Notes

- (b) (6): Welcome. Only a couple of topics on the agenda today: quick updates from the ACTIV-2 and ACTIV-3 teams and a discussion with ACTIV-2 leadership about their (b) (4) analysis plan. I do not have updated accrual polls so we will rely on the trial teams to provide these updates.

ACTIV-2 Trial Status

- (b) (6): ACTIV-2 currently has 70 active sites. The ACTIV-2 phase II open-label study is finished, and the phase III study is coming on board, with some sites already able to get IRB approvals to start enrolling participants in the phase III study.
- (b) (6) Version 2 of the ACTIV-2 master protocol was submitted to FDA Monday.

ACTIV-3 Trial Status

- (b) (6) Thank you. ACTIV-3 received final sign-off from FDA on version 2 of its (b) (4) last Friday. Training is planned for next Monday and Tuesday, with randomization of patients to start later next week. ACTIV-3 is pressing ahead with (b) (4) o agents. There is an issue with (b) (4) related to expiration of the drug.
- Submission of version 3 of the ACTIV-3 (b) (4) to FDA, in cooperation with (b) (4), is planned on or around December 14.
    - (b) (6): ACTIV-3 also received centralized IRB approval for version 2 of its protocol.
- (b) (6): ACTIV-3 leadership had initial discussions with the company producing (b) (4) to develop a plan to potentially onboard that drug. Because ACTIV-3 has been focusing on neutralizing antibodies (nAbs) in less severe hospitalized patients, there is an untapped resource within ACTIV-3 for high-flow nasal cannula (HFNC) and ventilated patients.
- (b) (6): (b) (4) should have topline results soon, and ACTIV-3 leadership may want to review those data prior to onboarding (b) (4). Is the Agent Selection Committee (ASC) looking at other agents for more advanced inpatients?
    - (b) (6): Currently only (b) (4) i.e., (b) (4). On (b) (4) may go out on their own as they did with (b) (4) The ASC continues to receive and consider other agents in that category. (b) (4) acalabrutinib is one example, but (b) (4) phase II study did not go well and acalabrutinib was ruled out.

  - (b) (6) : (b) (4) also lacked sufficient supply for ACTIV-3. (b) (4) research teams are looking at cyclosporin.
  - (b) (6) : (b) (4) is also on the ASC agenda for review. However, the large quantities necessary for effect do not look promising.
  - (b) (6) : The ASC is doing its due diligence on cyclosporin.
  - (b) (6) : The ASC can also review agents in the defer category to see if anything has emerged in the past month (when the deferred agents were last reviewed).
- (b) (6) Can I get clarification on the (b) (4) The TOC was previously told that part of (b) (4) study could not be funded by Operation Warp Speed (OWS), so arrangements were made with other appropriated funding sources. Then I heard that (b) (4) was able to have domestic manufacturing capabilities and could use OWS funds. Do you know one way or the other?
  - (b) (6) : OWS is still looking to NIAID to cover the cost of that agent.
- (b) (6) : In terms of (b) (4) , the company is doing their own phase IIb/III trial with (b) (4) They are projecting a fairly large effect size (hence the small number of patients). They are just about to get enrolled and ACTIV-3 will look carefully at that data before moving that agent into our trials.
  - (b) (6) : I agree, and there may be topline data or at least a trend available before that agent would enter ACTIV-3.
  - (b) (6) The company told us only 25% of the participants in the trial are in the HFNC or ventilated groups.

ACTIV-2 (b) (4) Data Analysis Plans

- (b) (6) : ACTIV-2 had a meeting with (b) (4) team about analysis of their agent. ACTIV-2 has data from patients in the (b) (4) and a full complement of participants in the (b) (4) dose. We agreed to look at data from the (b) (4) dose, both for the active agent and placebo, after last participant reaches day 28. Placebo data will help to evaluate the utility of the symptom diary, which will be important for the new phase III endpoint.
- For the (b) (4) dose, data analysis will be the same. We anticipate late January to February for that analysis to be done. The big question is how we put all of those data together for scientific communication. We will look at those (b) (4) data versus placebo first. If there is something interesting to be reported then we will do it; however, it is more likely we will include (b) (4) and (b) (4) data together.
- (b) (6) : Providers are already misunderstanding the *New England Journal of Medicine* article about the (b) (4) dose. If the (b) (4) dose works and is published prior to (b) (4) data, are you concerned this might cause providers to think they need 10 times the EUA for patient dose?
  - (b) (6) That was a big discussion point. We have agreed with (b) (4) that we will have few observations in the (b) (4) dose, especially if they are not consistent with the previous NEJM paper.
- (b) (6) : For the (b) (4) dose, when will you have virologic data?
  - (b) (6) : Viral loads by the end of next month, and resistance data are also coming. We are getting plasma samples to look at immune responses for both (b) (4) doses and thinking about how to analyze T-cell and B-cell responses. I will come back to the TOC to talk

  about that. (b) (4) requested a clinical study report for both doses, which will happen at the end of February.

  - If there is publication on 7 g data alone, everyone must agree, and we would revisit the TOC.
- (b) (6) : We want placebo arm data for the instrument because we want to revise the phase III endpoint for non-infused agents.
  - (b) (6) : We want to look at symptom data before day 28; if we wait until day 28 that would delay proposing a new endpoint to FDA.
  - (b) (6) : We are proposing a pooled analysis of symptom data from (b) (4) lacebo now, without breaking the blind, to design the next version of the protocol.
- (b) (6) : I think it's optimistic that you will see much of anything in outcomes from 45 people.
  - (b) (6) : We agree. Hopefully, we can see how the symptom diary is working.

ACTIV-2 Phase III Trial Endpoints

- (b) (6) The ACTIV-2 team is discussing changing the primary endpoint for ACTIV-2, phase III for non-infused agents (e.g., (b) (4) intramuscular dose of paired antibodies). Changing to a symptom-based endpoint will likely result in a significant decrease in the required sample size for phase III, but it is a significant change. John Farley noted FDA was anticipating that someone would propose this change. While there is precedent for flu, this change will require significant discussions with FDA because it would be precedent-setting for all other agents for mild to moderate COVID-19. FDA must weigh in, but we did not want to proceed without TOC approval.
- (b) (6) : This endpoint would still be focused on symptom duration. Currently, the definition is the last day during 28-day follow-up that participants report symptoms at a particular level, with that level depending on symptoms at entry. The change would be toward a simpler endpoint: time to consecutive days when all symptoms are resolved to a particular level.
  - (b) (6) : Given what is known about hospitalization rate for those not at high risk, having a hospitalization or death endpoint for studies that include low to moderate risk patients is not feasible for the number of participants that would need to be accrued. Therefore, for oral agents to have any impact, primary endpoints for participants with less severe COVID-19 must focus on acute symptom resolution, with long-term resolution as a secondary endpoint.
  - (b) (6) : In the (b) (4) study, with mixed moderate to severe patients, placebo hospitalization rate was on the order of 6 percent. In ACTIV-2, we anticipate a similar, if not lower, percentage of hospitalized participants, increasing the needed sample size per agent, which is not practical for multiple agents.
- (b) (6) : For (b) (4) 's study, in the high-risk group, hospitalizations were below 10 percent in the placebo arm and under 3 percent in the treatment arm. I think it is important to consider whether the product is financially viable. Is there a way to establish at what cost a treatment wouldn't be financially viable unless it prevented hospitalization, whereas for less expensive treatments (e.g., Tamiflu cost) a treatment that reduced symptoms might be viable?
  - (b) (6) : The new endpoint would only be for non-infused compounds, which should be less expensive.

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- (b) (6) : Another part of the ACTIV-2 new endpoint process is to generate a validated patient reported outcome (PRO) measure for the study diary. (b) (4) interviews (funded by (b) (4) the first step to a PRO, are in progress.
    - (b) (6) I think it's most important to nail down validity of the instrument and get agreement with FDA on the outcome measure as well as what is both a significant and clinically meaningful change in that outcome measure.
- (b) (6) : The ACTIV-2 team will come back to the TOC with finalized proposed new endpoints.
- (b) (6) : Because there needs to be a lot of thought and discussion before proceeding with the new endpoints, the ACTIV-2 team plans to open version 3 of the protocol (for the non-infused agents) with the original phase III endpoint. FDA discussions will continue while agents are in phase II, and the phase III endpoint will be modified after we get concurrence.
    - (b) (6) : ACTIV-2 must make it clear to the sponsors of non-infused agents that there will not be a seamless transition from phase II to phase III.
- (b) (6) : In addition, we have some measures for impact on transition and post-viral lung syndrome. The symptom diary may also be useful at long-term timepoints (e.g., 24- and 48-week).
- (b) (6) ACTIV-2 has TOC endorsement on its plan for both (b) (4) data analysis and phase III endpoint changes. Come back to the TOC when you have more granularity on the phase III endpoint.
- The latest timeline shows (b) (4) s entry into ACTIV-2 has shifted into December. The ACTIV-2 team is continuing to discuss the feasibility of onboarding five agents into ACTIV-2 in one month.

Appropriate Trial Network for (b) (4)

- (b) (6) : The first comment in the chat box from (b) (6) —about whether there is a reason NHLBI should not take the lead on the (b) (4) protocol—relates to an issue previously raised by the TOC and also discussed with Dr. (b) (6) about how NIH oversees studies going on outside of ACTIV at various ICs, including NHLBI, NIAID, and NCATS, and whether there needs to be overarching oversight across these studies. ACTIV-3 has been asked to look at (b) (4) . I don't have a strong feeling on this from a NIAID perspective but wanted to give others the chance to weigh in on this comment.
- (b) (6) : I think ACTIV-3 is better positioned to pick up another agent in January. Although I had did have a question about the plan for (b) (4) . There is a great efficiency with the shared placebo in ACTIV-3, but I am agnostic about which group takes the lead on (b) (4) .
    - (b) (6) : (b) (4) will be able to share a placebo with other ACTIV-3 agents because it is infused.
- (b) (6) : People from NHLBI that are part of CONNECTS serve on the ASC, and we have previously had conversations about who is best positioned to take on new agents. With CD24Fc, the ASC brought together individuals from ACTT, CONNECTS, and ACTIV-1 to determine who was able to take that agent on, and the collective decision was ACTT. Looking across the portfolio of studies, we felt ACTIV-3 was in the best position to take on another agent (b) (4)).
- (b) (6) : There are ICs targeting particular aspects of COVID-19 (e.g., viremia, host, lung, CV system). ACTIV-4 is up and running and agents that fit can be added to the ACTIV-4 master protocol. (b) (4)

targeting the lung cell and is designed to address an ARDS patient in a critical care environment, which aligns nicely with the NHLBI PETAL Network. I see an opportunity to ensure that different ICs can leverage their strengths.

- ○ (b) (6) [redacted]: A lot will depend on whether there is sufficient statistical power for these analyses because it seems that ACTIV-4A is looking more at thrombotic endpoints.
- ○ (b) (6) [redacted]: In addition, ACTIV-4 is a pragmatic trial (i.e., no placebo); I thought we wanted to test (b) (4) [redacted].
- ○ (b) (6) [redacted]: Those are valid points, and this is worth a conversation between these two main networks to ensure we have coordination on the (b) (4) [redacted] protocol. In addition, we need to ensure that there is coordination across NIH in the way protocols are identified, developed, and advanced so that each of these distinct programs has the opportunity to develop agents for which they bring the most expertise to bear.
- ○ (b) (6) [redacted]: I don't see why PETAL couldn't take lead on the (b) (4) [redacted] arm of this protocol; however, ACTIV-4A is a comparative trial and (b) (4) [redacted] needs a placebo-controlled registration trial. I think we need to separate the need for expertise on the trial design from the question of which trial is best suited to evaluate the hypothesis and generate the desired data. I would agree that pulmonologists have the best expertise to design the (b) (4) [redacted] protocol, but the ACTIV-3 trial design (or possibly ACTIV-5) is best suited to evaluate (b) (4) [redacted].
- ○ (b) (6) [redacted]: ACTIV-3 may be the best place to house (b) (4) [redacted] but I would like to ensure different teams have an opportunity to leverage their strengths. ACTIV is dealing with two of the NHLBI networks but CONNECTS has additional capabilities and sites that are not part of INSIGHT and could help with this kind of effort.

- (b) (6) [redacted]: I have two other points: (1) within ACTIV-3 leadership, which has representation from the PETAL and CTSN networks, one suggestion was having investigators from those networks as Co-PIs, and (2) whether to add a factorial for looking at (b) (4), (b) (5) [redacted] in critically ill patients, particularly after WHO released a guideline that (b) (4), (b) (5) [redacted] not be used in critical patients because it has no clinical value.
- (b) (6) [redacted]: I can organize a meeting for (b) (4) [redacted] similar to the one for CD24Fc, bringing together the relevant teams to determine which protocol is best suited to take on this agent. This can also be done in the future for other agents that don't obviously fall into a specific ACTIV protocol. I will reach out to the teams and get that meeting on the books.

Combat COVID Website

- (b) (6) [redacted]: The Combat COVID website launched yesterday. It's a soft launch, so no press and media until next week. Please go to combatcovid.hhs.gov (I have put this in the chat) and let the TOC know if there are any issues with the website so they can be remedied as fast as possible.
- (b) (6) [redacted]: Not sure if this is an issue, but (b) (6) [redacted] told me the contents of the website were not approved by the IRB. My understanding was that anything put forward to the public to facilitate enrollment of participants into clinical trials needed to be IRB approved.
    - ○ (b) (6) [redacted]: The website launch was on hold for a month waiting for IRB approval.
    - ○ (b) (6) [redacted]: For ACTIV-3, FAQs and scripts were sent through our IRB.

- (b) (6) She did say scripts were IRB-approved but website content itself was not.
- (b) (6) My understanding is that general inpatient information is ok. However, once individuals are directed to individual trial sites, those scripts are run by the IRB.

Chatbox (N/A)

From Jim Kiley to Everyone: 3:18 PM

Any reason why the NHLBI CONNECTS network shouldn't take the lead in the (b) (4) protocol? This targets the lung and sick patients in ICU, which is where our networks have lots of experience.

From Jens Lundgren to Everyone: 3:19 PM

Forgot to mention that first publication was accepted by NEJM on Tuesday

From Stacey Adam to Everyone: 3:19 PM

Congratulations, Jens!

From Judith Currier to Everyone: 3:20 PM

Congrats Jens and team

From Deydre Teyhen to Everyone: 3:20 PM

Congratulations Jens and team!

From Stacey Adam to Everyone: 3:20 PM

Jim, we had Taylor, Annetine and many of the PETAL and CTSN members on the call with the (b) (4) company

From Stacey Adam to Everyone: 3:21 PM

We will definitely be relying strongly on their expertise for this agent if it moves forward

From Jim Kiley to Everyone: 3:21 PM

Yes, I know, but CONNECTS in more than those 2 networks

From Jens Lundgren to Everyone: 3:21 PM

absolutely - PETAL and CTSN has profound expertise re ARDS

From Jim Kiley to Everyone: 3:25 PM

Yes, this is where CONNECTS and ACTIV are complimentary, but it seems this protocol aligns better with CONNECTS. Might want a further discussion as to who should lead it.

From Judith Currier to Everyone: 3:30 PM

In addition, impact on transmission will be important for these oral agents in early disease

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From Libby Higgs to Everyone: **3:47 PM**

(b)(4) came in through the antiviral team within the ACTIV Thx WG.

From Davey Smith to Everyone: **3:50 PM**

ACTIV-2 has brought in leads with other expertise for particular agents, like a crit care pulmonologist for the inhaled interferon

From Jim Kiley to Everyone: **3:53 PM**

thanks

From Stacey Adam to Everyone: **3:53 PM**

https://combatcovid.hhs.gov/

From Deydre Teyhen to Everyone: **3:53 PM**

https://combatcovid.hhs.gov/

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) met to discuss ACTIV-2 and ACTIV-3 updates, and to discuss development of an overall communications strategy for important trial updates.

Trial Status Updates

ACTIV-2

ACTIV-2 has thus far activated approximately 50 U.S. sites (zero ex-U.S. sites) and (b) (4), 81 of whom are on the (b) (4) dose (this dose has been approved to begin Phase III testing). Although patient demographics do not adequately represent minorities, rates of Black and especially of Latino enrollment are trending upward. The ACTIV-2 team has begun to develop a comprehensive plan to increase enrollment of Black participants into the trial.

The ACTIV-2 team has also decided to replace the Day 7 data analysis with a Day 28 analysis for the (b) (4) dose of the (b) (4) agent. FDA will soon provide input on this decision.

ACTIV-2 is not directly affected by the federal government's decision to advance purchase (b) (4) agent. However, Dr. (b) (6) noted that the ACTIV-2 team should consider developing a contingency plan for the possibility that FDA issues the agent an Emergency Use Authorization (EUA).

ACTIV-3

ACTIV-3 has thus far activated 51 sites, but following a DSMB meeting on October 26, all patient enrollment for the (b) (4) agent has ceased. The ACTIV-3 team, following the DSMB recommendation, will by November 9 submit for publication an interim report on its testing of the (b) (4) agent; it will also write a final report once the last patient has reached the 90-day follow-up timepoint.

The ACTIV-3 team will turn its focus toward opening sites and enrolling patients to test the (b) (4) (b) (4) Version 2 of the protocol. The team is ready to submit Version 2 for FDA and ethics review and will begin enrolling patients to administer both the new nAbs once these reviews are completed. Based on projections of patient accrual during Version 2 of ACTIV-3, the team expects to obtain interim safety and efficacy data by December.

The ACTIV-3 team is also set to proceed in developing Version 3 of the protocol, which will test (b) (4); it will begin discussions with both companies the week of November 2, with the expectation that the agents may enter the trial in December.

Discussion

Dr. (b) (6) noted that although all the agents that have been accepted into ACTIV-3 have different putative mechanisms of action, they have all been monoclonal nAbs; he indicated that if none of these agents demonstrates efficacy, then it may be worth considering accepting agents from other classes into the trial. Dr. (b) (6) suggested that (b) (4) may be interested in testing its agent in inpatients and emphasized—for any class of agent—the potential value of comparing different doses before an agent begins testing. Dr. (b) (6) will ask Dr. (b) (6), (b) (4) about (b) (4) 's potential interest in entering ACTIV-3. (b) (6) will also contact Dr. (b) (6) and Dr. (b) (6) to coordinate an ACTIV-3 leadership team call to discuss an agent prioritization strategy for future iterations of the study.

Topics for Discussion

Strategy for Communications about Significant Updates from ACTIV-2/-3

Considering the ACTIV-3 DSMB's recent recommendation to halt testing of the (b) (4) agent, the TOC discussed general strategy for communicating significant and potentially sensitive updates on ACTIV-2/-3 trials to various stakeholders (e.g., agent sponsors, the media). Dr. (b) (6) reported that, in the case of the (b) (4) agent, the DSMB met with trial leadership to recommend that the data be unblinded. Trial leadership received the DSMB's closed report, reviewed it, and then reconvened to develop a message that could be communicated publicly without producing confusion or risking misinterpretation. However, this message was developed solely by NIAID as the trial sponsor, along with (b) (4) representatives and the study team—no representatives from ACTIV or Operation Warp Speed (OWS) were involved in crafting or preapproving the message. NIAID has provided copies of the closed report to FDA and to (b) (4) Copies were also shared with Drs. (b) (6) and (b) (6), and with Dr. (b) (6) at FNIH.

Dr. (b) (6) proposed that the ACTIV-3 and ACTIV-2 teams communicate significant updates to each other in a timely manner, especially when updates relate to compounds that are being tested in both trials (e.g., the (b) (6) nAb). Dr. (b) (6) clarified that the lack of communication from ACTIV-3 to ACTIV-2 regarding the DSMB recommendation to cease testing of the (b) (6) agent was likely the responsibility of the NIAID communications office. He acknowledged the mistake and agreed that communications should be timely and consistent between the ACTIV-3 and ACTIV-2 trial teams, especially regarding agents being tested in both trials. Participants also agreed that DSMB meeting minutes sometimes take time to finalize before distribution, but Dr. (b) (6) emphasized the need for FDA to be informed of the bottom line of important DSMB decisions as quickly as possible (i.e., before meeting minutes are finalized).

Dr. (b) (6) proposed that the TOC outline a general communications plan to standardize how important updates about either ACTIV-2 or ACTIV-3 are relayed to various stakeholders, including points of contact for each of these stakeholders. Dr. (b) (6) and colleagues will draft this plan for the TOC to review. This communications plan can then be amended, as necessary.

Updates to Timing and Information

Dr. (b) (6) will update the slide presenting estimated timelines for product entry into trials to reflect that agents that were initially planned for October launch, but that have encountered delays (e.g., (b) (4) for ACTIV-2), will launch during November.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, NIAID, NIH*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID, NIH*

James P. Kiley, PhD, *Director, Division of Lung Diseases, NHLBI, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota and Principal Investigator, INSIGHT*

Sarah Read, MD, *Deputy Director, DAIDS, NIAID, NIH (WG Co-chair)*

Erica Ollmann Saphire, PhD, *Professor, La Jolla Institute for Immunology*

David (Davey) Smith, MD, *Professor of Medicine, U. California, San Diego*

Janet Woodcock, MD, *Therapeutics Lead, Operation Warp Speed*

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, *Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration (FDA)*

Elizabeth Church, PhD, *Deputy Director, Therapeutics Research Program, DAIDS, NIAID, NIH*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*

Helen Q. Chen, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received status updates on the ACTIV-2 and ACTIV-3 trials and discussed other topics escalated for its consideration, including ACTIV-2 contingency planning for (b) (4) s Emergency Use Authorization (EUA) request and ACTIV-3 contingency planning for the upcoming DSMB meeting, as well as brief updates from ACTIV leadership on clinical site recruitment and from the Agent Selection Committee (ASC) on (b) (4) ’s agent.

Trial Accrual and Status Updates

ACTIV-2

ACTIV-2 has opened 43 sites and (b) (4) , with most sites converted to the (b) (4) dose for (b) (4) drug. ACTIV-2 continues to open U.S. sites; there are currently no international sites. Patient enrollment continues to average 1 new participant per week. The ACTIV-2 team highlighted difficulties increasing enrollment due to the length of infusion times. However, some sites have shown significantly better recruitment (e.g., one Florida site has (b) (4) to date). The ACTIV-2 team is working to identify factors contributing to successful enrollment at these “superstar” sites that can be implemented at other study sites.

The Clinical Scientific Review Committee (CSRC) reviewed the ACTIV-2 protocol amendment (i.e., version 2), including the appendix for (b) (4) agent. Enrollment for the (b) (4) agent could begin as early as mid-November, pending submission of an Investigational New Drug (IND) application to FDA. To streamline the number of amendments and facilitate agent graduation from the protocol, the trial team plans to onboard agents once per month in groups. The team anticipates onboarding both (b) (4) eca’s agents simultaneously with the next protocol amendment (i.e., version 3). (b) (4) plans to enter ACTIV-2 with a (b) (4) dose; (b) (4) has minor issues to resolve (e.g., choice of placebo) for their agent.

ACTIV-3

ACTIV-3 has opened 50 sites and (b) (4) . Patient enrollment halted when the trial was paused by the ACTIV-2/-3 DSMB on October 13, but the team has continued to open sites while awaiting the next DSMB meeting on October 26. Several countries are approving version 1 of the ACTIV-3 protocol; regulators have been apprised of the upcoming DSMB meeting, but all are continuing to move forward.

The ACTIV-3 team assured the TOC that any determinations by the DSMB will be based on the best available data. They reported that the clinical sites have done excellent work to update the central database in preparation for the DSMB meeting, including collecting ordinal outcomes assessments for futility analysis as well as long-term follow-up data.

In parallel with the DSMB effort, the ACTIV-3 team is preparing version 2 of the study protocol. The Research Ethics Committee (REC) at The National Institute of Allergy and Infectious

Diseases (NIAID) Division of Clinical Research (DCR) completed a preliminary review of the protocol amendment, and the team is prepared to rapidly submit the amended protocol to regulatory agencies in all countries that have already approved version 1 of the protocol, including IND submission to FDA. In the amended protocol, remdesivir has been maintained as standard of care (SOC) in Appendix I, pending any further recommendations from various committees around the world. (b) (4) agents will be submitted with version 2 of the ACTIV-3 protocol. Entry of (b) (4) agent will be deferred, with conversations between the ACTIV-3 trial team and (b) (4) planned to commence in early November. Onboarding of (b) (4) 's agent is projected for December 2020 with version 3 of the ACTIV-3 protocol.

Discussion
The TOC discussed the tension between onboarding additional promising assets and delaying the entire trial by bringing in agents too rapidly. Thus, the TOC agreed that although the (b) (4) (b) (4) merits continued conversation between the company and the ACTIV-2 trial team, its trial entry should be delayed until phase I data are complete.

Regarding entry of (b) (4) agent, the ACTIV-3 trial team recommended engaging in cross-trial discussions. ACTIV-2 is planning to proceed with a (b) (4) IM dose and ACTIV-3 has discussed onboarding with two (b) (4). The TOC agreed it would be preferable to synchronize these efforts in order to track the full spectrum of potential outcomes. Because (b) (4) will not enter ACTIV-2 or ACTIV-3 with the next round of amendments, Dr. (b) (6) will arrange a call between (b) (4) and both trial teams in early November.

Topics for Discussion

ACTIV-2 Contingency Plan if (b) (4) Receives EUA Approval

The TOC and ACTIV-2 team discussed a series of contingency plans for enrollment of patients and randomization of patients to placebo based on the outcome of (b) (4) EUA request.

Enrollment of Patients to the (b) (4)
Some TOC members felt enrollment for (b) (4) agent should be discontinued if an EUA is granted, in particular because (b) (4). However, the TOC agreed that several other factors argue for continuing enrollment, including anticipated delays with distribution and difficulties with administration of (b) (4) drug under the EUA. In addition, discontinuing enrollment for (b) (4) monotherapy may make it more difficult to enroll patients in ACTIV-2 unless another agent (e.g., (b) (4)) is ready to begin enrollment. Separately from these immediate trial considerations, continuing enrollment would perform a public service (by providing access to the treatment while distribution and administration issues in the general healthcare system are resolved) and would gather additional data on virology toward ACTIV's long-term goals.

Randomization to Placebo
Some TOC members felt that continuing to randomize patients to placebo could create a mixed message for the public while other members felt it would be difficult to generate safety data

without a control arm. One TOC member suggested a possible mechanism by which patients could receive the (b)(4) drug without unblinding if they progressed (i.e., became hospitalized). The TOC agreed there was not yet enough information to determine whether randomization should continue, but the right options were available pending FDA's decision on (b)(4) s EUA.

Early Release of ACTIV-2 Data for (b)(4)

The TOC previously raised the prospect of unblinding ACTIV-2 data for (b)(4) . However, ACTIV leadership expressed concern that in a randomized trial with a shared placebo, releasing endpoint-driven data before a study's endpoint was reached could harm clinical equipoise. While some TOC members shared this concern, others emphasized the value of learning as much as possible from early data given the gravity of the pandemic, noting that both (b)(4) have released early data without consequence. The TOC recommended that the ACTIV-2 team seek input from the DSMB at their November 9 meeting and report back to the TOC before unblinding any data.

ACTIV-3 Contingency Plan for DSMB Meeting Results

Based on the outcome of the DSMB meeting, ACTIV-3 will either continue to enroll patients or it will not. If ACTIV-3 continues enrollment, then it will submit the protocol amendment with additional agents.

Trial Amendment

The biggest unknown identified by the ACTIV-3 trial team was whether the DSMB will indicate that the protocol needs to be changed.

New Agent Onboarding

If the DSMB determines that there may be a class effect, that determination could impact onboarding of agents similar to (b)(4) in the ACTIV-3 pipeline. It would also open a conversation about unblinding the (b)(4) data. The TOC agreed that if the DSMB decides to halt treatment with (b)(4) drug due to a safety signal, then it would be necessary to unblind the data. The TOC has now made two requests to (b)(4) to share safety data with the DSMB for ACTIV-3 and (b)(4) . The TOC agreed to postpone any further conversation until after the DSMB meeting.

Update from ACTIV Leadership Meeting

At the request of ACTIV leadership, FNIH is continuing to engage (b)(4) for clinical site recruitment. In addition, Dr. (b)(6) has now received responses from 5 to 6 NIH Institutes and Centers (ICs) regarding his request for additional clinical sites that could be leveraged for ACTIV trials. Dr. (b)(6) reported ACTIV is also continuing to move forward with (b)(4) , noting the non-disclosure agreement (NDA) is almost complete.

ASC Update on (b)(4)

The TOC asked the ASC to review additional data for (b)(4) conditionally approved agent after the trial teams flagged issues with (b)(4) (b)(4) '. (b)(4) indicated (b)(4) was not duplicated in a (b)(4) study, but they did not provide the supporting data. Dr. (b)(6) noted

(b) (4) agent also showed (b) (4) in sections of human spinal cord and other central nervous system (CNS) tissues; however, it is not clear whether the signal is cytoplasmic or membranous. In addition, the trial team noted (b) (4) agent has a significantly shorter half-life than mAbs with a wild-type Fc.

The ASC developed the following list of requests/questions that has been sent to (b) (4) for their response: (1) provide data that show binding was an artifact due to “denaturation of proteins”; (2) provide evidence that the binding is not unexpected; and (3) provide data showing the location of mAb binding at the cellular level (i.e., does the sponsor know if the mAb is binding to neurons in the CNS or spinal cord). In addition, the ASC requested data from the (b) (4) study as well as any information pertaining to (b) (4) from (b) (4) IND discussions with FDA. The ASC’s opinion is that while the initial (b) (4) data raises concerns, if (b) (4) provides data from a second study showing no (b) (4) and can show that FDA has not raised concerns about (b) (4) data, then the agent can move forward.

While half-life itself is not an issue, the ASC considered that (b) (4) may play a role in the shorter half-life. Therefore, they also asked (b) (4) to provide any evidence of the following issues that may affect half-life: (1) development of anti-drug antibodies (ADA), (2) kinetics of tissue distribution during the first hours after dosing; and (3) artifactual effect of last timepoint measurement (i.e., only day 7 data were reviewed by the ASC). The ASC requested data from the scheduled day 14 measurement to analyze half-life more fully. The ASC had no concerns about overlapping antigen binding domains, noting factors other than binding affect an agent’s capacity for neutralization. The TOC agreed to discuss the (b) (4) agent again after receiving all the requested data.

Appendix A: Participants List

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Austin Van Grack, MS, *Committee Coordinator, Social and Scientific Systems*

Rachel Harrigan, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems*

Col. Deydre Teyhen, DPT, PhD, *Director of Therapeutics, Operation Warp Speed*

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Helen Q. Chen, *Consultant, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) received brief updates on both ACTIV-2 and ACTIV-3 trials and discussed other topics escalated for its consideration, including trial capacity and agent prioritization. In response to (b)(4) initial submission for Emergency Use Authorization (EUA) of their monotherapy, the TOC discussed implications for ACTIV-2 and ACTIV-3 trials. The TOC also reviewed the status of neutralizing antibody (nAb) product shipments and agreements with (b)(4) and the U.S. Government (USG).

Trial Accrual Updates

The TOC received brief status updates on ACTIV-2 and ACTIV-3 accruals and timelines.

ACTIV-2

ACTIV-2 has opened 33 sites and (b)(4). Sites are active in 25 states and Washington D.C. The (b)(4) product began enrolling patients in ACTIV-2 phase II in August; products from (b)(4) are expected to enter phase II in late October/early November, with (b)(4) following in December. The ACTIV-2 trial team emphasized enrollment of new sites is increasing, with five sites added yesterday and more anticipated next week.

ACTIV-3

ACTIV-3 has opened 44 sites and (b)(4). In addition to expanding sites in the U.S., it has opened eight sites in Denmark as well as one site in Singapore. (b)(4) single monoclonal antibody (mAb) therapy has entered the ACTIV-3 protocol; agents from (b)(4), (b)(4) and possibly (b)(4) are poised to enter in October, and (b)(4) (b) (4) mAbs are expected in early December. The ACTIV-3 team expected the (b)(4) agent to reach the 300-patient mark later this week, at which point the DSMB will consider expanding the enrollment criteria and enter the agent in to Stage 2. The DSMB will meet October 26 to make its recommendation to the trial team. In addition, the trial team projects (b)(4) per week going forward, scaling up to 100 patients per week as the number of trial sites increases.

Topics for Discussion

(b)(4) Press Conference: Request for EUA

Based on interim data from the (b)(4) held a press conference to announce the submission to FDA of an initial EUA request for their monotherapy (b)(4)) in higher-risk patients. They anticipated submitting a subsequent EUA request for their combination therapy (b)(4) in November. (b)(4) also announced plans to initiate a pragmatic, open-label clinical trial, enrolling patients treated with either the monotherapy or the combination therapy, in October 2020. Dr. (b)(6) advised the TOC that FDA would likely deliver its decision on the initial request within two weeks.

The TOC discussed potential paths forward for ACTIV-2/-3 trials if (b)(4) EUA is approved. Some members felt continued data gathering had little clinical utility if an EUA is granted; however, the TOC agreed that pausing the trial had significant disadvantages (e.g., impacts on enrollment and delays in re-initiating sites).

The TOC agreed to continue to enroll patients in the placebo-controlled study until FDA issues a decision on the EUA for the (b)(4) monotherapy. Patients will be transferred to the (b)(4) dose as soon as that change can be operationalized. If the EUA is approved, ACTIV will continue to recruit patients to the (b)(4) arm, transitioning to an open-label study and collecting additional safety and virologic data without placebo. TOC members also considered the addition of a separate non-inferiority study for higher-risk patients using (b)(4) monotherapy as the standard-of-care (SOC) comparator, noting that this approach would likely require revision of clinical endpoints. While FDA's decision is pending, ACTIV trial teams will work to add new arms for other approved agents as quickly as possible.

Trial Capacity

The TOC briefly discussed funding and trial capacity. Dr. (b)(6) shared the National Institute of Allergy and Infectious Diseases (NIAID) perspective, which supports continued funding of ongoing clinical trials. Once monotherapies are established, additional research will be necessary to determine combination treatments with the greatest efficacy.

Assuming continued funding, the ACTIV-2 trial team anticipated capacity for 8 agents in phase II and 5 agents in phase III. The trial team noted the ACTIV-2 pipeline currently exceeds this capacity and therefore recommended that no new agents be evaluated or approved unless they are superior to currently approved agents in some aspect (e.g., route of administration). The approval of new agents for ACTIV-2 would come at the expense of those agents already approved. Thus, TOC members agreed letters should be sent to all companies with agents in the ACTIV pipeline that convey *entry into ACTIV-2 cannot be guaranteed at this time.* Letters should also be sent to companies with submissions pending evaluation that communicates *ACTIV is unable to evaluate any further agents at this time*.

The ACTIV-3 trial team anticipated capacity for 2 to 3 agents before the end of the calendar year, depending on the outcome of (b)(4) EUA request. However, the team hesitated to definitively state the trial was at capacity because an influx of US sites is anticipated in the near future and overall capacity for ACTIV-3 should increase after the new year.

The TOC recommended considering what other types of assets should be explored if/when ACTIV feels nAbs have been exhausted. Dr. (b)(6) noted the Agent Selection Committee (ASC) has developed a nAb crosswalk organized around asset diversity to aid these discussions, emphasizing the diversity of agents already in the ACTIV pipeline.

Prioritization of Approved Agents

In response to the TOC request, the ASC developed scientific criteria for prioritizing approved agents, including independent testing, rapidity of escape, and diversity (e.g., product type, effector function, route of administration, and antigen/binding domain). They also identified operational criteria for prioritization: enrollment, equity, and manufacturing and availability of compounds. TOC members will review and approve these criteria after the meeting.

The TOC discussed whether additional agents requiring intravenous infusion should be studied in the low-risk outpatient population, given the difficulties involved in broadly implementing this route of administration, or whether agents with alternate routes of administration should be prioritized instead. Potential alternate routes of administration, based on agents in the ACTIV pipeline, include intramuscular (b)(4) and inhaled (b)(4). Dr. (b)(6) also noted that a company with an oral compound in an ongoing phase II study has expressed interest in the ACTIV-2 phase III trial.

Dr. (b)(6) provided a brief status update for the (b)(4) agents. (b)(4) will soon have additional safety data for a 300 mg/kg dose and is waiting for internal regulatory approval for intramuscular delivery. ACTIV trial teams have been meeting weekly with (b)(4) regarding their inhaled IFN-beta product. Members of the ACTIV-2 trial team felt weekly touchpoints were adequate to accelerate the (b)(4) agent into ACTIV-2.

Dr. (b)(6) offered to follow up with (b)(4) regarding the status of their internal regulatory approval for intramuscular delivery.

Study Controls

TOC members advocated against matching placebos to each route of administration to avoid the accumulation of control groups that cannot be shared. Dr. (b)(6) noted that FDA has already approved the use of shared placebos for ACTIV-1 and members of the ACTIV-2/-3 trial teams agreed that matching placebos were not needed for all routes of administration.

Status of Independent Testing by (b)(4) and USG

The TOC reviewed the status of agreements and materials for independent (b)(4) and USG testing.

Dr. (b)(6), (b)(4) reported that (b)(4) has received executed contracts and materials from (b)(4) has executed contracts but has not yet received materials from (b)(4); it has received materials from (b)(4) but contracts are still under legal review. The contract with (b)(4) is almost complete.

Dr. (b)(6), (b)(4) reported that USG labs have completed the necessary paperwork with all manufacturers and should receive the last of the companies' samples next week. The first (b)(4) has been completed, with products from (b)(4) and initial in vitro data should be available next week. (b)(4) was not able to submit materials in time for the first study but should start the study next week; Dr. (b)(6) will share an update on (b)(4) status at next week's meeting.

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Helen Q. Chen, *Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*

Kelly E. Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

David Goff: **00:30:46**

Might they use infusion centers that are currently doing chemo?

Stacey Adam: **00:31:11**

Hi David, we are discussing this with NCI.

Davey Smith: **00:32:24**

Home health can also be used for infusions

David Goff: **00:33:53**

Any chance of getting the combo therapy they want to market?

Davey Smith: **00:34:34**

They do not have enough any time soon, I think

Janet.Woodcock: **00:35:44**

FDA has to let them do home infusions. I'm trying to find out if that would be allowed, (b)(4) does not have data from home infusion. jw

Davey Smith: **00:36:33**

Good point. They will be asking for home infusions, I think

Janet.Woodcock: **00:37:42**

Yes, I would. It is much more practical

Erica Ollmann Saphire: **01:06:22**

Stacey - if you're turning new antibodies and companies away, please send them to (b)(4) We have 110+ mAbs to evaluate side-by-side and would be happy to evaluate novel ones to see if they are superior to or different from what exists. (b)(4) would help mobilize an agent/cocktail identified in the (b)(4) study.

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) met to receive ACTIV-2 and ACTIV-3 updates, discuss topics escalated for TOC discussion, and review agents under consideration.

Trial Status Updates

ACTIV-2

ACTIV-2 has (b) (4) and thus is fully enrolled for Phase II testing of the (b) (4) (b) (4). It next will move to Phase III open-label testing of this Ab, which will persist until (b) (4) agent enters the trial. Enrolled patient demographics are diversifying, although the current percentages are misleading because the denominator includes all patients who did not specify any race/ethnicity (the ACTIV-2 team is working to generate more accurate patient demographic statistics). Thus far, ACTIV-2 has activated 68 sites.

ACTIV-3

ACTIV-3 is still paused, although FDA is now reviewing Version 2 of the protocol. Once Version 2 is approved by FDA it will advance for central U.S. IRB review. The ACTIV-3 team expects that by the week of November 23, previously activated sites will reactivate to launch Version 2.

Topics for Discussion

(b) (4) Participation in ACTIV-3

Dr. (b) (6) asked TOC members to share their thoughts on whether ACTIV-3 should proceed with incorporating this agent into its trials. (b) (4) was recently asked to pause enrollment of the most severe COVID-19 patients into its neutralizing Ab trial, which suggests that interim clinical data may indicate lack of efficacy, or even potential harm to critically ill patients. Dr. (b) (6) noted that a follow-up DSMB meeting is scheduled to occur before December to review updated trial data. Dr. (b) (6) proposed that ACTIV wait for the results of that DSMB meeting and seek to obtain underlying data from the (b) (4) trial before deciding whether to pursue the agent for ACTIV-3. Participants agreed with this approach and noted that ACTIV teams can continue their discussions with (b) (4) in the meantime, but that the ACTIV-3 team should hold on producing a protocol amendment for the agent. Dr. (b) (6) will also ask the ASC to weigh in on the new data from the (b) (4) study in combination with the (b) (4) data to see if they would make a recommendation for severe COVID-19 patients.

Dr. (b) (6) emphasized the importance of clearly communicating this decision to all affected ACTIV teams and subteams. Participants also agreed that the ACTIV-3 team will communicate the TOC's decision during its December 4 meeting with (b) (4)

Effects of Monoclonal Ab Treatment on Immune Response to Vaccines

Dr. (b) (6) stressed the need to conduct sub-studies of monoclonal Ab clinical trials to investigate how monoclonal Ab treatment might affect immune response to vaccines. Dr.

(b) (6) noted that the ACTIV-2 team is planning to conduct such a study using samples from Phase II testing of the (b) (4) Ab, but that the team needs funds to launch the study. Dr. (b) (6) noted that FDA could likely provide these funds, but the ACTIV-2 team will need to coordinate with NIAID to establish a funding mechanism. Dr (b) (6) is also planning to conduct separate vaccine trial sub-studies of patients who have received monoclonal Ab treatment to further explore the effects of such treatments on vaccine response. He envisioned that this sub-study could be funded via an R01 grant, but Dr. (b) (6) advised against an R01 because of the need to launch studies quickly.

Dr. (b) (6) stressed that the most important goal for these studies will be to investigate how monoclonal Abs for prophylaxis affect noninfected people's immune responses to vaccines. Dr. (b) (6) suggested that CoVPN might be best suited to conduct these studies. Dr. (b) (6) noted that other studies should also investigate how natural immune responses to monoclonal Abs affect vaccine responses, and how patients who first received a monoclonal Ab and then were infected with SARS-CoV-2 respond to a subsequent vaccine. Dr. (b) (6) agreed to convene a group of ACTIV and non-ACTIV researchers to discuss protocol designs for these various studies, and she will also contact Dr. (b) (6) to learn more about his envisioned Ab/vaccine interaction studies. As study plans for these investigations become more firmly established, study design teams will send Dr. (b) (6) estimated costs so that she can mobilize the funds required.

Participants acknowledged that very large studies would be required to answer these scientific questions with clinical data, and agreed to proceed on the assumption that serologic samples can be used to identify a correlate of protection that can help answer these questions without large clinical studies. Dr. (b) (6) will determine whether the (b) (4) study incorporates any investigation of Ab/vaccine interactions.

Amended Communications SOP/Plan

Dr. (b) (6) will circulate a graphic depicting the revised ACTIV Cross-Trial Communications Process. Participants will review the graphic offline and provide their comments and feedback.

Coordination of Inpatient COVID-19 Trials

Dr. (b) (6) suggested establishing a forum for leadership from ACTIV, Operation Warp Speed, NIAID, NHLBI, and NCATS to coordinate efforts across ongoing inpatient COVID-19 trials, mainly to identify the top-tier questions for these trials to address and to ensure that trial designs are coordinated to address them. Participants agreed that such coordination is important to fill scientific gaps and avoid duplication of efforts across ongoing inpatient trials.

Possible Plan for Data Analyses for ACTIV-2

Dr. (b) (6) will send Dr. (b) (6) Possible Plan for Data Analyses for ACTIV-2 in PDF format to all TOC members, who will review the document for discussion during the November 25 TOC meeting.

Agent Reviews

(b) (4)

The Antiviral Subteam reviewed (b) (4) which is intended to protect severely ill patients who have developed ARDS and found evidence of significant clinical benefit. The Subteam proposed entering the agent into ACTIV-3, to be administered to patients on high-flow oxygen and others in the trial's first stratum who are not eligible for monoclonal Abs. TOC members need to determine whether this agent should be incorporated into ACTIV-3. Dr. (b) (6) supported the agent's entry, but stressed that the TOC should wait until up-to-date clinical data become available 28 days after last patient enrollment (Dr. (b) (6) confirmed that perhaps 18 or fewer days are needed to reach that timepoint). Dr. (b) (6) will circulate the current data package for this agent by November 19 and will schedule a meeting with the company for November 23 to give the ACTIV-3 trial team time to review the data package beforehand.

Single Monoclonal Abs

The ASC is currently reviewing two single monoclonal Abs: (1) (b) (4) and (2) (b) (4) The ASC has requested additional data on (b) (4) Ab for further review, and the TOC will receive an ASC recommendation once those additional data have been reviewed. The (b) (4) Ab is inhaled and appears to be potent, although the ASC continues to await further data. ACTIV could facilitate the creation of combinations of Abs from multiple companies but determining appropriate pairings would require more information (e.g., binding epitopes) on each agent. Dr. (b) (6) also noted that the ASC is maintaining an Ab crosswalk to track how candidate Abs overlap to assist evaluation and prioritization of agents.

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Helen Q. Chen, *Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

David Goff: 38:44

I can provide a little context about what NHLBI is doing.

ACTIV, Cross-trial Operations Meeting

Thursday, October 15th, 2020

Action Items

Action Items		
	Information	**POC**
1	Seek support from (b) (4) for site assessment	**David Wholley / Paul Stoffels**
2	Consolidate site lists from (b) (4) and from ACTIV-3/McKinsey	**David Wholley / Rachel Harrigan**

Meeting Summary

- The group celebrated the recent launch of ACTIV-1, ACTIV-4 and ACTIV-5
- While ACTIV-3 is on pause per DSMB recommendation, team will continue the ongoing efforts around the “controllables”, including site registration, PR, co-enrollment, collecting and disseminating lessons learned, etc.
- The ACTIV leadership is exploring additional partnership with (b) (4) and NCORP to identify additional top-performing sites for ACTIV studies
- Industry partners can potentially donate personnel and technology tools to support ACTIV efforts
- Team is in discussion with CVS Health around leveraging the Minute Clinics and Home Health services for patient referral and follow-up for ACTIV outpatient trials

Notes

ACTIV Trials Launch Update

- ACTIV-1 launched on October 15
- ACTIV-4
  - Pre-hospitalized and hospitalized cohorts were launched on September 17
  - Hospitalized cohort has (b) (4) as of October 14
- ACTIV-5
  - Activated Emory this week
  - Started BET-A (Risankizumab, an anti-IL23)
  - Holding (b) (4) pending additional review of (b) (4) for potential class effect

ACTIV-3 DSMB Recommendation

- Stacey Adam provided an overview of the ACTIV-3 DSMB recommendation and discussed the operational implications

- Deydre Teyhen: What can we do in these 2 weeks, i.e., control the controllables? Supporting existing sites? Double down on site identification and activation?
- Laura McNay: Priority is to get sites registered – those that are currently in the portfolio and additional ones we are seeking out
- Rachel Harrigan: Team held a solutioning meeting yesterday to progress other solutions - PR, co-enrollment, activating ex-US sites, deep dive in central vs. local IRBs, collecting and disseminating lessons learned (i.e., identification of real bottlenecks for the site activation process)

Leadership Update

- Janet Woodcock, Francis Collins, and Paul Stoffels met on October 14 and discussed what else can be done to assist the study teams and identified ways industry can support
- (b) (4) has a list of sites with ratings and performance – (b) (6) discussed with (b) (4) leadership and they are willing to share that list to identify additional top-performing sites that are not currently in our networks
    - Deydre Teyhen: In addition, team has compiled a list of registered sites used in (b) (4) studies from Clinicaltrials.gov
    - Jane Atkinson: It takes a while to vet through the list to identify eligible sites with the appropriate capacity, personnel, experience, and expertise. It would be helpful to have industry partners filter through and conduct assessment
    - Lynn Marks: Focus now is to explore how to operationalize – what would happen and what are the roadblocks
    - Dave Douglas: It would be helpful to determine what kind of data the database contains – that would help inform the type of legal requirements needed
    - Rachel Harrigan: ACTIV-3 has been working with McKinsey to collect and filter sites – efforts need to be coordinated
- Francis Collins engaged with NCI Community Oncology Research Program (NCORP), who has a network of community-based hospitals that can conduct trials
- Paul Stoffels plans to engage with industry partners to see if they are willing to succumb personnel to assist with site activation
    - ACTIV study teams expressed interest
    - For ACTIV-2: Would need to work out with PPD
    - Would need to work out the contracting vehicle to operationalize
        - Tony Punturieri: Industry is also running a lot of trials - how to navigate the fine line between government-funded trials and their own trials
        - Janet Woodcock: Would avoid conflict of interest - can't have their asset in the same trial they are helping with, etc.
- Thomas Stock: Industry also has tools to optimize study performance

ACTIV, Cross-trial Operations Meeting

Thursday, October 15th, 2020

Hot Topics Discussion

- HHS Portal Update
    - Landing page to link to trial websites or contact information from a single POC
    - Chris Shreeve requested information the following information:
        - Recruitment goal for each of the study
        - List of active trials, with contact person
        - Any promotion in terms of paid media
- Met with (b)(4) to discuss potential partnership (mostly with outpatient trials)
    - ACTIV-4b
        - 100-200 (b)(4) that can do rapid testing and blood draws to be used as actual sites for ACTIV-4b
        - Additional 300 sites for screening, testing, and referrals
        - Follow-up through (b)(4)
        - Dave Douglas: #1 would be helpful - enables a completely remote process; #2 and #3 would be helpful if bundled together
        - Tony Punturieri: ACTIV-4 team is also talking with a (b)(4)
    - ACTIV-2
        - "Swab-and-send" in the (b)(4) and refer information to ACTIV-study and sites within 30 miles
            - Bill Erhardt: Is (b)(4) going to charge? ACTIV-2 team is also in conversation with (b)(4) so want to benchmark
            - Stacey Adam: Has not formally discussed cost but suspect referral process would be free, as testing cost is covered by other mechanisms
        - (b)(4) (infusion centers) can potentially be leveraged for drug administration
            - Peter Kim: (b)(4) would augment the vendor ACTIV-2 is exploring. Do they have bandwidth?
            - Stacey Adam: (b)(4) is cognizant but confirmed it is not an issue, as they are wrapping up a few trials

Chatbox

From Laura M to Everyone: 09:27 AM
ACTIV 3 would be all in!

From Jane Atkinson to Everyone: 09:29 AM
ACTIV-1 would be very interested in activation help.

From Sarah Dunsmore to Everyone: 09:29 AM
Industry-led site activation teams may not be the best fit for the ongoing inpatient convalescent plasma trials but we would certainly try to be OPEN to all optimization strategies

From Kevin Bugin to Everyone: 09:58 AM
Given the time, we can share via the meeting notes/email information on the RDV ex-US shipping question, including best practices/procedures. And, we can discuss the question on supporting a central procurement v. individual procurement.

High-Level Meeting Summary

Representatives of all ACTIV trial teams convened to receive trial status updates, including updates from the most recent Leadership Team meeting; hear a presentation on stress management tools for trial leadership; and see a demonstration of the enrollment simulation tool that is now available to all ACTIV trial teams.

Action Items

- Dr. Judy Hochman will send Dr. Stacey Adam the ACTIV-4A appendix when completed.
- Dr. Peter Kim will email Dr. Paul Ridker information about a company that may be able to provide a rapid-turnaround PCR-based assay.
- Trial leaders will respond to Dr. Adam's email soliciting availability for a webinar to engage other potential NIH clinical trial networks in ACTIV trials.
- Col. Deydre Teyhen will send the third stress management checklist to Dr. Adam, who will resend the complete set of checklists to ACTIV trial leadership teams.

Stress Management Tools

Col. Deydre Teyhen, OWS

In her previous role as Commander of the Walter Reed Army Institute of Research, Col. Deydre Teyhen oversaw the Center for Military Psychiatry and Neuroscience, which conducts studies of brain and behavioral health that range across parameters such as sleep, resilience, and mindfulness. This research has helped quantify the impact that good leadership can have on stress mitigation and health outcomes. During wartime, for example, good leadership can reduce rates of post-deployment PTSD diagnoses, while during COVID-19, it has increased mask wearing among soldiers from 57 to 77.3 percent (a 20 percent change) and increased COVID-19-related self-monitoring from 48.7 to 75.2 percent (a nearly 30 percent change). Drawing on this research, Col. Teyhen outlined small actions ACTIV trial leaders can take to have a large impact on their teams' mental health.

Adapt Communications to the Pandemic

Create a Simple Information-Sharing Routine

Regularly sharing information about pandemic-related activities and priorities helps team members orient themselves in an overwhelming situation. Col. Teyhen, for example, sends her team a brief update each morning that is organized to enable skimming.

Offset Virtual Meetings with One-on-One Connections

While virtual platforms have allowed meetings to continue during the pandemic, these virtual meetings are vulnerable to in-person and digital interruptions. Leaders should think deliberately about how to forge connections with team members outside these platforms, such as through an occasional text message or a 5-minute check-in focused purely on a team member's needs.

Account for Disruption

Incorporate Team Limits into Quality Control Processes

Stress can decrease people's ability to process complex information and thus increase the risk of error. Leaders can help teams manage this risk by clearly designating high- and low-priority actions to allow people to pace their work; building a robust checks-and-balances system that distributes responsibility for catching mistakes; and reacting with patience when more time is needed or errors do occur.

Control the "Controllables"

Leaders can help their teams work through the enormity of the pandemic by guiding them to recognize and focus their activities on elements that they can control and by articulating a vision of how these activities will impact long-term outcomes.

Use Checklists

Checklists can help leaders easily incorporate stress management techniques into their team interactions without placing increased burden on their own pandemic workloads and stress levels. Three easy-to-use checklists are available from Col. Teyhen.

Directly Address Team Member Stress

Explicitly Encourage Physical and Psychological Resilience

Leaders should make resilience an explicit part of their messages to their teams. Physical resilience incorporates not only healthy sleep and nutrition but also the pursuit of safe outdoor activities; psychological resilience includes not only mindfulness and time management techniques but also efforts to achieve a healthy level of news consumption, so that daily pandemic developments do not overwhelm the people involved in this effort to overcome it.

Normalize Stress

Leaders can explicitly recognize high stress levels as a completely normal and universal response to the pandemic. This normalization gives team members permission to discuss stress management as a component of their professional activities. Leaders should also make deliberate space for these discussions to take place.

Seize the Moment

Although the pandemic increases stress levels, trial team members' efforts to address it of course have great value, and the experience of that value can help offset stress. Leaders should remind ACTIV participants that they are helping to solve a problem that has not been encountered in living memory, and that they are doing it at a critical moment when the U.S. faces not only the worst pandemic since 1918 but also the greatest social unrest since the 1950s and the greatest financial stress since the 1930s. The import of their work can help teams maintain focus and purpose.

Trial Status Updates

ACTIV-1

ACTIV-1 has opened 4 sites and (b)(4). Forty U.S. sites have been identified (out of 60 ultimately needed), but site activation continues to pose a challenge. Additional ex-U.S. sites have been identified in South America. The trial team is amending its protocol to allow co-enrollment with ACTIV-4 and to account for FDA approval of remdesivir. It also continues to monitor discussions of whether remdesivir should remain the study's standard of care.

ACTIV-2

ACTIV-2 has opened 53 sites and (b)(4). It continues to test the (b)(4) of the (b)(4) agent while the company's EUA is under consideration and is planning the graduation of that agent to Phase III. The next agent from (b)(4) will be added to the protocol in November, after the company resolves IP issues. The ACTIV-2 team cautioned that trial teams should take care in incorporating extraneous activities into ACTIV trials: after initially agreeing to help (b)(4) collect data for future PK, ADA, and hyperreactivity analyses, the ACTIV-2 team found that the kit supply chain sometimes hindered site activation and enrollment and thus it has now allowed sites to skip this step when doing so preserves the pace of the trial.

ACTIV-3

ACTIV-3 had recruited 326 patients when the DSMB recommended halting accrual to the (b)(4) compound. Although differences in safety outcomes between the experimental and placebo group were not significant, the threshold for identification of activity was not met. The ACTIV-3 team has reviewed unblinded data and will continue to conduct follow-ups until day 90; it will release both a preliminary and final report.

The trial team is submitting Version 2 of the ACTIV-3 protocol on October 30, which will allow co-enrollment with ACTIV-4 and will onboard two new agents from (b)(4) These agents are scheduled to enter the trial by the week of November 9, with first safety assessment likely in mid-November (at 60 to 80 patients) and feasibility assessment likely in December (at 450 patients). Version 3 of the protocol will include an mAb from (b)(4), which is currently completing its Phase I trial, and may include (b)(4), as well.

ACTIV-3 has analyzed patient subgroups to assess whether dose timing has affected outcomes. Across three subgroups defined by time from symptom onset to study enrollment (under 5 days, 7 days, or over 9 days), no statistical or visual differences were observed.

ACTIV-4

ACTIV-4A has activated 11 sites and (b)(4) The team has queued 150 total sites but is working through a slow activation process. ACTIV-4A is completing a new appendix with a third trial arm to test an anti-platelet P2Y12 inhibitor both alone (in patients with average risk for bleeding) and in combination with full and prophylactic dose heparin (in patients with low risk). ACTIV-4A is also working on co-enrollment with ACTIV-1 and on a transition of discharged patients into ACTIV-4C.

ACTIV-4B has (b)(4) at 2 sites. Although no new sites have joined the protocol over the last month, the recent selection of a CRO is expected to expedite contracts with 30 to 50 sites identified by the (b)(4) and the identification of more sites to meet the ultimate goal of 250. The ACTIV-4B trial team is working with (b)(4) to enable at-home collection of venous blood on recently diagnosed patients nationwide and is piloting a novel process that allows ACTIV-4B to coordinate a remote trial enrollment process for any (b)(4) patient who meets trial criteria. NHLBI has also arranged access to the desktop (b)(4), a point-of-care testing device that will ultimately be available to all sites. Dr. (b)(6) cautioned that the (b)(4) platform may generate false positives.

ACTIV-4C is finalizing preparations for activation. The protocol has been reviewed by the DSMB and the trial team is responding to FDA comments. Initial drug shipment will begin on November 6 and sites will open shortly thereafter.

ACTIV-5

ACTIV-5 has opened 1 site and has 2 more likely to onboard during the week of November 2 with others scheduled to follow. (b)(4) patients have been enrolled.

ACTIV Partnership Leadership Meeting Update

Stacey Adam, FNIH

ACTIV leadership has recognized and is concertedly addressing site activation and enrollment challenges described by all trial teams. At the most recent Leadership Team meeting, ACTIV participants presented four major challenges and existing efforts to address them:

1. Site Identification and Assessment – efforts include forecasting and predictive analytics
2. Site Activation – efforts include administrative augmentation, recruitment of HHS volunteers, and broader external partnerships
3. Enrollment – efforts include PR campaigns, CEAL collaboration, an HHS portal, and patient referral programs
4. Trial Execution – efforts include leadership communication and staff augmentation

Leadership Team members identified additional paths to address these challenges, which are already being actively pursued. These paths include:

- Connecting Dr. Janet Woodcock with CEOs of additional major healthcare organizations to identify potential clinical trial sites
- Collaborating with the industry group (b)(4), which (at the instigation of Dr. Paul Stoffels) is identifying potential trial sites within its database and has connected ACTIV with the (b)(4) to discuss additional sites and with the (b)(4) discuss possible staff augmentation
- Collaborating with (b)(4)) is assessing potential support for ACTIV clinical operations or for ACTIV's engagement with international regulatory bodies

- Connecting with the (b)(4) study team at (b)(4), which (b)(4) will share enrollment lessons learned from its large COVID-19 studies
- Pursuing an expanded patient referral partnership with (b)(4)
- Streamlining communication across the clinical trial ecosystem

A webinar is also being scheduled to facilitate conversations between ACTIV trial teams and potential trial networks affiliated with NIH Institutes and Centers.

Lessons from the ACTIV-2 Dose Transition

Peter Kim, Davey Smith, and Judith Currier, ACTIV-2

The ACTIV-2 team recently transitioned from a (b)(4) dose of (b)(4) agent. The team's effort was streamlined by the fact that the new dose did not require new packaging; sites were able to use one existing vial of drug in place of the previous ten vials. However, several other factors also smoothed the transition and other ACTIV teams may consider these factors during their own potential future transitions.

Amendment Strategies

The ACTIV-2 team coordinated closely with regulatory colleagues to strategize the fastest and most convenient way to conduct its transition. Because the team was transitioning from one *dose* to another rather than from one *drug* to another, it was able to file a letter of amendment rather than a formal amendment, which expedited the approval process.

In selecting amendment strategies, trial teams need to weigh tradeoffs between immediate and long-term efficiency. Incorporating multiple protocol changes in a single amendment can streamline the number of amendments required over the long term. However, because elements of an amendment cannot be severed during the approval process, a single unimportant element of a complex submission can delay approval of another urgent update.

Unique constraints affect amendment planning for international protocols. Dr. Bill Erhardt noted that although many ex-U.S. regulatory authorities have expedited first submissions of COVID-19-related protocols, they have *not* extended expedited status to protocol amendments; therefore, teams may opt to delay their initial protocol submission to reduce the need for a planned amendment soon thereafter.

Leveraging a Single IRB

Once ACTIV-2 received regulatory approval for its dose change, the team leveraged the trial's single IRB structure to operationalize the transition. Upon IRB approval, the ACTIV-2 CRO immediately circulated a document laying out operational changes to all sites, and as soon as that document was signed, the new dose could be delivered immediately.

Accrual Simulation Tool

(b) (6) [redacted] (b) (4) [redacted]

Following this meeting, the ACTIV accrual simulation tool will be available on Basecamp to all trial teams. The tool uses a set of (b) (4) [redacted].

(b) (4) [redacted]

Dr. (b) (6), (b) (4) [redacted] presented a demonstration of the tool, which is a (b) (4) [redacted]

Although the demonstration focused on ACTIV-2, Dr. (b) (6), (b) (4) [redacted] noted that the tool is fully adaptable to all ACTIV Trials. A User Guide is included in the access package on Basecamp.

(b) (4) [redacted]

(b) (4) [redacted]

Appendix A: Participants List

TRIAL TEAM MEMBERS

ACTIV-1

William G. Powderly, MD, *ACTIV-1 Chair and J. William Campbell Professor of Medicine, Director of the Institute for Clinical and Translational Sciences, Washington University in St. Louis*

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Lisa LaVange, PhD, *Professor and Associate Chair, Department of Biostatistics, UNC Chapel Hill*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

ACTIV-2

David (Davey) Smith, MD, *ACTIV-2 Chair Professor of Medicine, U. California, San Diego*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Michael Hughes, PhD, *Professor, Department of Biostatistics, Harvard University*

Cyrus Javan, MD, MPH, *Medical Officer/Program Officer, Division of AIDS, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS, NIAID*

ACTIV-3

James D. Neaton, PhD, (not in attendance) *ACTIV-3 Chair and Professor of Biostatistics, University of Minnesota*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen*

Birgit Grund, PhD, *Associate Professor of Statistics, University of Minnesota*

ACTIV-4

Judith S. Hochman, MD, *ACTIV-4A Chair and Harold Snyder Family Professor of Cardiology, Department of Medicine, NYU Grossman School of Medicine*

Paul Ridker, MD, *ACTIV-4B Chair; Senior Physician, Brigham and Women's Hospital; Eugene Braunwald Professor of Medicine, Harvard Medical School*

Tom Ortel, MD, PhD, (not in attendance) *ACTIV-4C Chair and Chief, Division of Hematology, Department of Medicine, Duke University*

Scott Berry, PhD, *Adjunct Professor, Department of Biostatistics & Data Science, Kansas University Medical Center*

Jean Connors, MD, *Associate Professor, Department of Medicine Brigham and Women's Hospital*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI, NIH*

Eric Leifer, PhD, (not in attendance) *Mathematical Statistician, NHLBI, NIH*

Allison Morris, MD, *ACTIV-4D Co-Chair and Professor of Medicine, Immunology, and Clinical and Translational Research, University of Pittsburgh*

Frank C. Sciurba, MD, *Professor, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh*

Abdus Wahed, PhD, *Professor, Department of Biostatistics, University of Pittsburgh*

Clinton B. Wright, MD, *Director, Division of Clinical Research, National Institute of Neurological Diseases and Stroke (NINDS), NIH*

ACTIV-5

John Beigel, PhD, *Division of Microbiology and Infectious Diseases, NIAID, NIH*

OPERATION WARP SPEED

Tom Stock, DO, *Clinical Advisor to ACTIV-1 and Former Vice President, Clinical Development and Operations, Pfizer*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, MD, *Clinical Advisor to ACTIV-3 and Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

David Douglas, *Clinical Advisor to ACTIV-4 and Former Head, Global Research and Development Project Management Office, Pfizer*

Ciaran Lawlor, PhD, *OWS Consultant, Boston Consulting Group*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

Sheri Parker, PMP, PhD, *CAPT, MSC, USN, Therapeutics Clinical Operations Director, Operation Warp Speed*

Ritika Philip, *OWS Consultant, Boston Consulting Group*

Col. Deydre Teyhen, *DPT, PhD*, *Director of Therapeutics, Operation Warp Speed*

NATIONAL INSTITUTES OF HEALTH

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases*

TX-CLINICAL WORKING GROUP

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-Chair)*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

Helen Q. Chen, PhD, *Senior Consultant, Deloitte*

OTHER INVITED ATTENDEES

Krishna Deepak, MS, *Consultant, Boston Consulting Group*
Raahul Ramakrishnan, MD, *Project Leader, Boston Consulting Group*
Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems*

STAFF

Evan Appell, *Consultant, Deloitte*
Alex Sorosa, *Consultant, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From deydre.teyhen to Everyone 01:03:12

New PR just out, https://investor.regeneron.com/news-releases/news-release-details/regn-cov2-independent-data-monitoring-committee-recommends

IDMC recommended halting the cohorts with high flow O2 or MV in the hospitalized study due to safety concerns. This was an ad hoc informal meeting and will be followed up at the formal IDMC review Nov 18th.

From Stacey Adam to Everyone 01:03:41

Thanks, Deydre!

Accelerating COVID-19 Therapeutic Interventions and Vaccines

ACTIV Partnership Leadership Group Meeting

April 22, 2020, 10:00 – 11:00 am ET

April 22, 2020

This meeting summary was prepared by Lucas Smalldon, MA, Rose Li and Associates, Inc., under contract to the Foundation for the National Institutes of Health (FNIH). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of FNIH.

High-Level Meeting Summary

The Leadership Group overseeing the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened to review progress made since program launch on April 3, 2020. Dr. Francis Collins, Director of the National Institutes of Health, opened the meeting by reviewing ACTIV's overall aims and current status. Following Dr. Collins' review, the Leadership Group received updates from Co-Chairs of all four ACTIV Working Groups (WGs), which cover the following focus areas: (1) Therapeutics-Preclinical; (2) Therapeutics-Clinical; (3) Clinical Trial Capacity; and (4) Vaccines. The Group discussed significant progress toward identification and prioritization of preclinical and clinical compounds, development of a master protocol and inventory of potential networks for ACTIV trials, and planning for broad data sharing to facilitate vaccine development.

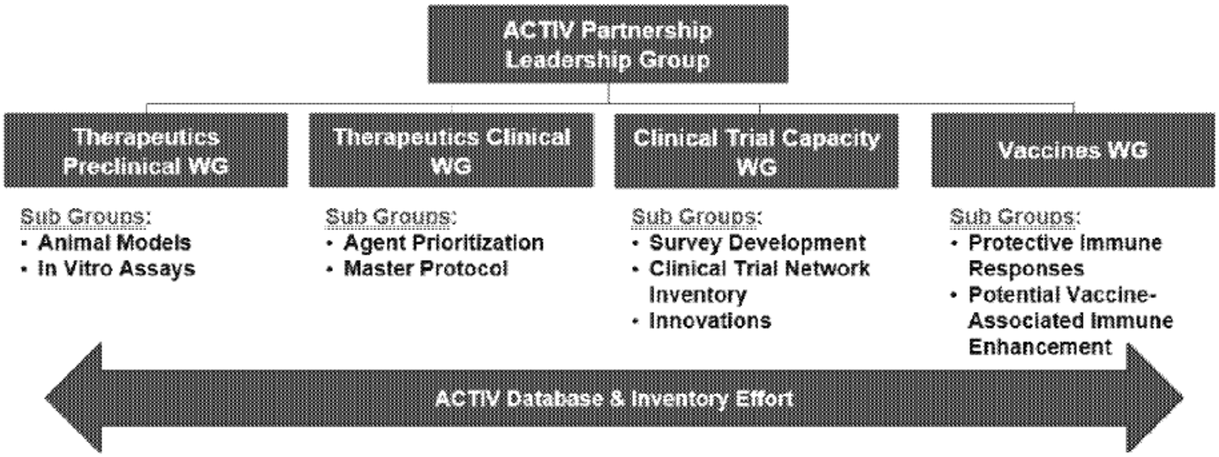
ACTIV's Overall Aims and Current Status

Francis Collins, MD, PhD, Director, NIH

On April 3, in response to the emergence and rapid spread of the SARS-CoV-2 virus and of the Coronavirus Disease 2019 (COVID-19), leaders from NIH, the biopharmaceutical industry, the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA), as well as academic researchers, launched the ACTIV public-private partnership. ACTIV aims to respond rapidly to the COVID-19 crisis by developing a coordinated biomedical research and development strategy to address the pandemic, creating a framework for prioritizing vaccine and drug candidates most likely to succeed in preventing and treating COVID-19, establishing a streamlined infrastructure for conducting clinical trials of promising therapeutic agents and vaccines, and coordinating regulatory processes while leveraging available assets, expertise, and financial resources among all partners.

Based on these aims, the Leadership Group decided during its April 3 meeting to establish four rapid action Working Groups (WGs) in each of the following focus areas: (1) Preclinical Therapeutics, (2) Clinical Therapeutics, (3) Clinical Trial Capacity, and (4) Vaccines. Since that initial meeting, these WGs have moved quickly to launch activities in their respective focus areas, including establishing Subgroups to pursue more specific goals within each area. The WGs will provide updates to the ACTIV Partnership Leadership Group every 2 weeks.

The graphic below captures ACTIV's current structure. ACTIV Database and Inventory Efforts referenced in the figure include projects across the WGs to compile inventories of relevant data, such as available compounds, studies underway, available *in vitro* assays and animal models, Biosafety Level-3 and -4 (BSL3/4) facilities, and clinical trial network capacity.


ACTIV Partnership Leadership Group
Therapeutics Preclinical WG
Sub Groups:
• Animal Models
• In Vitro Assays
Therapeutics Clinical WG
Sub Groups:
• Agent Prioritization
• Master Protocol
Clinical Trial Capacity WG
Sub Groups:
• Survey Development
• Clinical Trial Network Inventory
• Innovations
Vaccines WG
Sub Groups:
• Protective Immune Responses
• Potential Vaccine-Associated Immune Enhancement
ACTIV Database & Inventory Effort

ACTIV is also coordinating with various other COVID-19 response efforts, including the ACCORD project in the UK, the (b) (4) [redacted] COVID-19 Therapeutics Accelerator, and the COVID-19 R&D Leaders Consortium, as well as with federal agencies such as CDC and the (b) (4) [redacted]

Therapeutics-Preclinical WG

Christine Colvis, PhD, National Center for Advancing Translational Sciences (NCATS); John Young, PhD, Roche

The Therapeutics-Preclinical (TX-Preclinical) WG will create an integrated preclinical framework to evaluate drugs and drug candidates that have been in human trials for potential repurposing. The WG has established Animal Models and Screening Assays Subgroups to inventory these resources and has created a preliminary list of BSL 3/4 facilities (documenting each facility's capacity). The WG is also working with the Therapeutics-Clinical (TX-Clinical) WG to develop criteria for rapidly prioritizing preclinical compounds.

The WG has (b) (5) [redacted] in conducting rapid COVID-19 therapeutic and vaccine research, including limited availability of some testing resources (b) (5) [redacted] enabling studies for COVID-19 therapeutics.

To address these challenges, the TX-Preclinical WG is (b) (5) [redacted]. Although some of these activities will require input from external stakeholders, the TX-Preclinical WG anticipates completing most of them during May, and (b)(5) by mid-June, potentially by (b)(5).

Discussion

Dr. (b)(6) noted that, given the large number of antibodies now entering clinical trials, it could be beneficial to establish a repository to share features of antibodies currently being tested (e.g., epitope and antibody format) to inform development of antibodies for future testing waves.

Therapeutics-Clinical WG

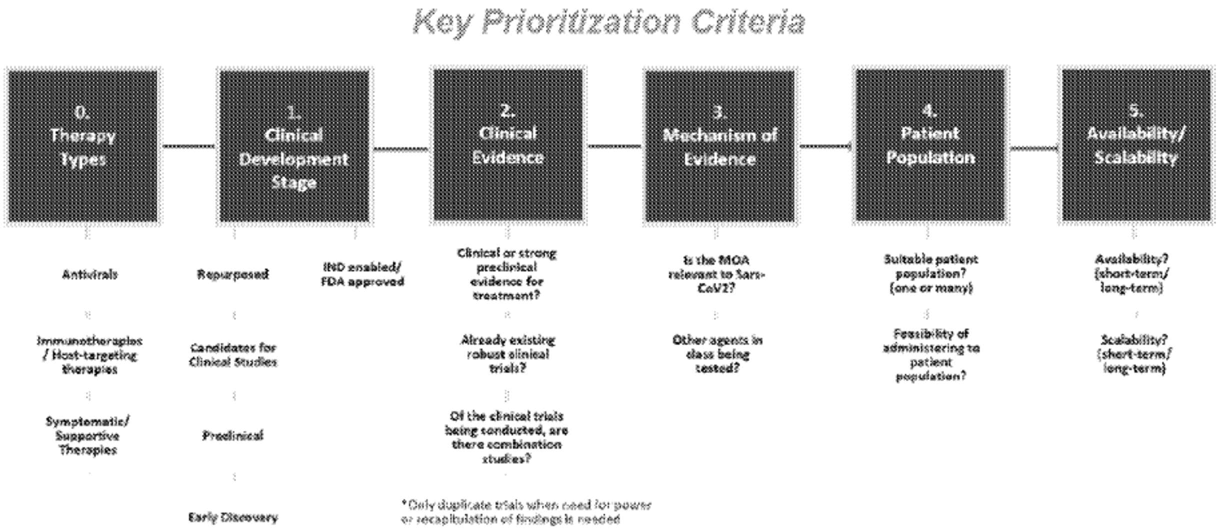
Eric Hughes, MD, PhD, Novartis; Sarah Read, MD, National Institute of Allergy and Infectious Diseases (NIAID)

The TX-Clinical WG has decided to prioritize therapeutics for target patient groups in the following order: (1) hospitalized/moderately ill (non-ICU) and critically ill/ventilated (ICU); (2) outpatient/ambulatory ill; and (3) unaffected (prophylaxis). The WG established two Subgroups to move therapeutics toward clinical trials: Agent Prioritization and Master Protocol development.

Agent Prioritization Subgroup

The Agent Prioritization Subgroup decided to consider compounds in three primary classes: (1) antivirals; (2) immunotherapies; and (3) symptomatic/supportive therapies. The Subgroup has defined prioritization criteria for all agent classes, which will inform development of a Master Protocol to test them.

The TX-Clinical WG is now collecting data needed to evaluate agents against the prioritization criteria; it has also collected several existing inventories of compounds with potential applicability to COVID-19. The WG will prioritize all potential agents in waves: (1) FDA-approved or IND-enabled agents; (2) clinically ready agents; (3) current preclinical agents or agents targeting prophylaxis. During each wave, the WG will classify agents by mechanism of action (MOA) and will eliminate those agents or mechanisms already being adequately tested in other clinical trials. A shortlist of agents will then be submitted to a small Expert Panel that will use the WG's Agent Prioritization Criteria (shown in the diagram below) to select agents for clinical trials under a master protocol in suitable patient populations.


Key Prioritization Criteria
0. Therapy Types
1. Clinical Development Stage
2. Clinical Evidence
3. Mechanism of Evidence
4. Patient Population
5. Availability/ Scalability
Antivirals
Immunotherapies / Host-targeting therapies
Symptomatic/ Supportive Therapies
Repurposed
Candidates for Clinical Studies
Preclinical
Early Discovery
IND enabled/ FDA approved
Clinical or strong preclinical evidence for treatment?
Already existing robust clinical trials?
Of the clinical trials being conducted, are there combination studies?
*Only duplicate trials when need for power or recapitulation of findings is needed
Is the MOA relevant to Sars-CoV2?
Other agents in class being tested?
Suitable patient population? (one or many)
Feasibility of administering to patient population?
Availability? (short-term/ long-term)
Scalability? (short-term/ long-term)

Master Protocol Subgroup

The agent prioritization criteria shown above align with the Master Protocol Subgroup's 'hybrid' master protocol approach, which will involve two parallel processes: (1) amending the existing NIAID-sponsored Adaptive COVID-19 Treatment Trial 2 (ACTT2) protocol (i.e., producing an "ACTT3" protocol) to allow rapid testing of repurposed drugs at existing ACTT2 sites with established standard operating procedures, and (2) designing a *De Novo* ('Gold Standard') Master Protocol to address ACTIV's more comprehensive goal of continuously testing promising therapeutics under a single protocol for all three patient populations of interest.

The *De Novo* master protocol will enable adaptive trials with a shared standard of care (SOC) arm, which could be adapted to new evidence; harmonize endpoints with existing COVID-19 master protocols; support the addition of new agents as they become available; streamline data collection to reduce site burden; operate under a central Institutional Review Board and Data Safety Monitoring Committee; and function under a single IND held by a neutral third party.

Discussion

Deprioritized agents will be continuously reassessed for testing during subsequent prioritization waves as more data become available. The TX-Clinical and TX-Preclinical WGs will coordinate to ensure that data generated from preclinical testing are funneled into prioritization discussions.

Clinical Trial Capacity WG

Elizabeth Desrosiers, MS, PMP, Merck; Michael Kurilla, MD, PhD, NCATS

The Clinical Trial Capacity WG aims to maximize capacity and optimize efficiency of clinical trials in order to expedite testing of prioritized candidate therapeutics for COVID-19. To achieve these goals, the WG has established three Subgroups: (1) Clinical Trial Network Inventory; (2) Survey Development; (3) Innovations.

Clinical Trial Network Inventory Subgroup

The Clinical Trial Network Inventory Subgroup has created a preliminary inventory of 38 existing clinical trial networks along with their known capabilities and capacities. It has divided networks into three tiers according to how quickly they may feasibly begin conducting ACTIV clinical trials (Tier 1: fully functional in 6 weeks or less; Tier 2: fully functional in 6 to 12 weeks; Tier 3: fully functional in more than 12 weeks). Of 38 networks inventoried, 25 are grouped under Tier 1.

Survey Development Subgroup

The Survey Development Subgroup has worked with the TX-Clinical WG to determine the capabilities and capacities required for networks and sites to conduct successful clinical trials under ACTIV's *De Novo* master protocol. It has begun adapting these capabilities and capacities into survey questions to circulate among the networks and sites identified by the Inventory Subgroup. Survey responses, which will ultimately be recorded in a database, will help the Clinical Trial Capacity WG determine the most suitable networks and sites to conduct ACTIV clinical trials and ideally match candidate compounds to specific sites or networks. The survey will also identify what SARS-CoV-2 trials are currently underway at the various sites of interest. The Subgroup plans to begin circulating the survey to networks and sites on April 24.

Innovations Subgroup

The Innovations Subgroup is working to assess current COVID-19 studies to learn from failures and successes, and to apply those lessons learned to future ACTIV studies. Although inpatients remain ACTIV's top priority, this Subgroup is also assessing current studies of other patient populations in multiple care settings (e.g., ambulatory, prophylaxis, home care) to identify innovative ways to improve study design (e.g., remote monitoring).

Discussion

The WG Co-Chairs clarified that they are focused mainly on US-based networks right now, although some of those networks include international sites.

Vaccines WG

Kathrin Jansen, PhD, Pfizer; Douglas Lowy, MD, National Cancer Institute (NCI)

The Vaccines WG aims to coordinate vaccine development programs and to develop a regulatory pathway that will reduce the standard registration timeline by several months. Several vaccines have already entered clinical trials in the US and elsewhere, and more will enter trials soon. Whereas typical vaccine development involves years of studying a virus and designing suitable candidates, vaccine development for SARS-CoV-2 must proceed rapidly.

The accelerated timeline to develop a SARS-CoV-2 vaccine imposes several challenges. Vaccine development programs must continuously make key decisions amid constantly changing evidence and without some relevant information (e.g., protective titers). This process makes it difficult to balance the benefits of rapid development of effective vaccines with unacceptable risks to patient safety. To address these challenges, the Vaccines WG will aggregate and share information and resources across vaccine development efforts, housing them in a centralized repository so that key decisions benefit from up-to-date, thorough, and accurate information.

The Vaccines WG has established two subgroups focused on ongoing efforts related to (1) protective immune responses and (2) potential vaccine-associated immune enhancement. Each subgroup is now aggregating key information to help inform decisions by efforts in each of these areas.

Subgroup 1 is identifying information sources as well as sharing platforms and processes to help aggregate and circulate the following information:

- Natural history data on COVID-19 to potentially identify a protective immune response
- Assay methods (e.g., to distinguish among vaccine responses for SARS-CoV-2 and other coronaviruses to help characterize protective immune response)
- Animal models to inform whether vaccine-induced responses are adequate

Subgroup 2 is aggregating existing bodies of evidence from animal models and human testing of other viruses including coronaviruses, synthesizing present understandings of potential vaccine-associated immune enhancement, and identifying approaches to monitor for potential immune enhancement in studies.

Discussion

Participants noted the possibility of learning from plasma therapy trials to define correlates of SARS-CoV-2 protection. For example, identifying levels of neutralizing antibody titers that have a therapeutic effect against SARS-CoV-2 could help investigators to characterize what vaccine-induced responses need to be achieved in clinical settings. In addition, vaccine development efforts should aim to target components of SARS-CoV-2 that exhibit limited variability to maximize effectiveness against as many virus strains as possible. Minimizing target variability is particularly important because SARS-CoV-2 is an RNA virus that mutates rapidly. Moreover, it is critical for research groups to share sequences from virus strains detected around the globe as soon as possible to inform vaccine development efforts.

Regulatory Input

Dr. Janet Woodcock emphasized the need to conduct adaptive Bayesian trials with seamless Phase II to III transitions for COVID-19 patients and affirmed FDA's willingness to coordinate with ACTIV to support those efforts.

Next Steps

Lists below capture next steps for each WG, with anticipated completion dates for each action.

TX-Preclinical WG

- Define the prioritization approach for animal use, assay selection, and staging of testing by April 29.
- Finalize the inventory of animal models, assays, and BSL 3/4 facilities by May 8.

TX-Clinical WG

- Gather necessary resources to develop Drug Repurposing master protocol and begin drafting protocol on April 24.
- Decide on a design for the *De Novo* master protocol, gather resources, and begin drafting by April 30.
- Finalize prioritization criteria by April 24 and prioritize potential agents by April 30.

Clinical Trial Capacity WG

- Deploy network survey on April 24.
- Finalize inventory of Tier 1 networks by April 22.
- Finalize inventory of Tier 2 and 3 networks by May 13. Deploy survey by May 14.
- Finalize innovations for the Drug Repurposing master protocol amendment by May 8.

Vaccines WG

- Define specific activities for protective immune responses and potential vaccine-associated immune enhancement by April 27.
- Establish knowledge sharing platforms for vaccine developers by May 1.

Appendix A: Participants List

Francis Collins, MD, PhD, *Director, National Institutes of Health (NIH) (Session Leader)*
Christopher P. Austin, MD, *Director, NCATS, NIH*
Marco Cavaleri, *Head of Office, Anti-infectives and Vaccines, EMA*
Christine Colvis, PhD, *Director for Drug Development Partnership Programs, National Center for Advancing Translational Sciences (NCATS), NIH*
Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*
Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*
Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*
Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*
Maria Freire, PhD, *President and Executive Director, FNIH*
Jordan Gladman, PhD, *Health Program Specialist, NIH*
Thomas J. Hudson, MD, *Vice President of Oncology Discovery and Early Development, AbbVie*
Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*
Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*
Michael Kurilla, MD, PhD, *Director, Division of Clinical Innovation, NCATS, NIH*
Douglas Lowy, MD, *Principal Deputy Director, National Cancer Institute (NCI)*
Mathai Mammen, MD, PhD, *Global Head, Research & Development, Johnson & Johnson*
John Mascola, MD, *Director, Vaccine Research Center, NIAID, NIH*
David Meeker, MD, *KSQ Therapeutics (formerly Genzyme)*
Hitesh Pandya, MD, *Respiratory Physician, AstraZeneca*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*
Steven Paul, MD, *Chief Executive Officer and Chairman of the Board, Karuna Pharmaceuticals*
Roger M. Perlmutter, MD, PhD, *EVP and President, Merck Research Laboratories*
Guido Rasi, *Executive Director, European Medicines Agency (EMA)*
Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*
Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*
Daniel M. Skovronsky, MD, PhD, *Senior Vice President and Chief Scientific Officer, Eli Lilly and Co.*
Lawrence Tabak, DDS, PhD, *Principal Deputy Director, NIH*
Julie Tierney, JD, *Chief of Staff, Center for Biologics Evaluation and Research, FDA*
John Tsai, MD, *Head, Global Drug Development and CMO, Novartis*
William Pao, PhD, MD, *Head, Pharma Research & Early Development, Roche/Genentech*
Andrew S. Plump, MD, PhD, *President, Research and Development, Takeda*
John C. Reed, MD, PhD, *EVP, Global Head: Research, Sanofi*
Herbert (Skip) Virgin, MD, PhD, *EVP Research and CSO, Vir Biotechnology*
Janet Woodcock, MD, *Director, Center for Drug Evaluation and Research (CDER), FDA*

John Young, PhD, *Global Head, Infectious Diseases, Roche*

Stacey Adam, PhD, *Science Program Manager, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate VP of Science, FNIH*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Margaret Anderson, *Managing Director, Deloitte*
Nina Gonzalez, *Senior Manager, Deloitte*
Elizabeth Kim, *Senior Consultant, Deloitte*
Rosa Marie Alvarez, *Consultant, Deloitte*
Benjamin Stratton, *Senior Consultant, Deloitte*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*

Appendix B: Zoom Chat Transcript

(b) (6) **30:14**

use this chat box if you want to raise a question

(b) (6) **32:00**

I have a suggestion for this subgroup regarding a repository to share preclinical data re antibodies entering the clinic

(b) (6) **37:05**

I believe that groups should also publish clinical antibodies in a peer reviewed format. While this is not standard, the current circumstance is different. This is not being consistently done to date.

(b) (6) **38:14**

to add to this the sharing of real time data with regard to convalescent serum infusion data would also be helpful

(b) (6) **38:30**

+1

(b) (6) **40:25**

This is a really good idea. Also the banking of small amounts of pooled plasma from various trials so that one can compare the properties of transfused materials in a consistent fashion across studies. For SARS there was variation in the assays used to characterize plasma used for infusion.

(b) (6) **40:57**

Do the animal models recapitulate the ARDS seen in critically ill COVID-19 patients?

(b) (6) **41:16**

only partially

(b) (6) **41:25**

Re this subgroup i was wondering how we’d also get the list of deprioritized assets?

(b) (6) **42:50**

I have not seen that on ARDS in animals to date. Note also that the NHP models often do not specify the extent of the pathology across the lung and the actual clinical respiratory function. Thus whether they are disease models is not yet clear? Maybe others know this.

(b) (6) **44:33**

For SARS-COV2 there are no established models for severe disease

(b) (6) **45:15**

Why different population could not be studied in parallel?

(b) (6) **45:20**

Marco is correct - mild clinical scoring for the NHPs, some infiltrates on imaging

(b) (6) **j 46:34**

It will be important to engage network investigators in choosing next therapeutic that will enter studies, rather than being prescriptive.

(b) (6) **48:19**

What about the “cytokine storm”-like pathology associated with severe COVID-19 infection? Do the animal models recapitulate? Are these models suitable for testing anti-inflammatory mechanisms or mostly useful for testing anti-virals?

(b) (6) **50:24**

As severe illness is associated with a lot of cytokine secretion it will be important to understand what inflammatory responses are protective versus pathologic. The initial clinical trials can lend some depth/specificity to the concept of storm.

(b) (6) **51:56**

regarding this it would be good to get data from patients on anti-inflammatories for other diseases (MS, IBD etc) who get infected with COVID-19 and see how they fare versus matched controls not on those agents

(b) (6) **53:15**

observational databases based upon EHR or claims data are usually 6 months behind in data cleaning--to be useful they need to overcome this lag.

(b) (6) **54:40**

are these international or US networks?

(b) (6) **55:15**

Can we access across EPIC-users for these data in real time?

(b) (6) **56:46**

Skip's question is being actively pursued currently

(b) (6) **58:50**

the NIAID vaccine and clinical trial networks are global in scope re South America and Africa especially Sub Saharan Africa. It is unusual to have Europe in most of the NIAID networks

(b) (6) **01:01:20**

Can the plasma therapy trials be used to define correlates of protection? If one assumes therapy has a relationship to prophylaxis- this may be rapid.

(b) (6) **01:01:58**

Is there any specific reasons why clinical efficacy trials are not included in the scope?

(b) (6) **01:04:05**

they are a given but we do not know if by the time a vaccine is ready for an efficacy evaluation the attack rates are still high enough to prove efficacy; having supportive animal challeng data may be helpful

(b) (6) **01:04:06**

Are the plasma therapy trials actually randomized trials or are they ad hoc therapy done on a local level? There is also an IgG immune globulin being made is that being put into the master protocol as an RCT?

(b) (6) **01:04:50**

We should share efforts to model then simulate required levels of antibody titers to be protective - can use convalescent serum AND animal data AND therapeutic antibody data in one model.

(b) (6) **01:05:21**

agreed they are a given and should be included

(b) (6) **01:06:17**

the use of surrogate endpoints for vaccine coupled w human safety and early signs of protection may be the most powerful way to accelerate vaccines to approvals; how do we align cross teams on this in the best way

(b) (6) **01:07:05**

would human challenge models be considered?

(b) (6) **01:07:06**

best alignment might come from common DSMB that also looks at correlates data and events across trials as they progress.

(b)(6) **01:07:36**

NAID is willing to convene this umbrella DSMB, though potential correlate ideas should come from biopharma partners.

(b)(6) **01:08:24**

Strong support for surrogate endpoints for vaccines!

(b)(6) **01:09:07**

agreed therefore the emphasis on animal models, serological assays etc

(b)(6) **01:09:14**

NIAID agrees- we'll want to dig into this more deeply.

(b)(6) **01:09:22**

A recent open publication report from the Sinovac inactivated virus as vaccine suggested low likelihood for antibody dependent enhancement of disease. whats the views of this finding and any other reports in this space soon emerging

(b)(6) **01:10:04**

Assuming plasma therapy is effective, would we consider directly testing the correlation by administering plasma from vaccinated individuals to the clinically ill and monitoring for response. It would tell us in perhaps a more rapid fashion the immune response is relevant.

(b)(6) **01:10:11**

There are plans/ proposals to put together centralized labs and statisticians experienced in correlates of protection to allow cross protocol analyses and hence the desire to have harmonized efficacy trials. This would allow the ability to develop a correlate of protection sooner; a benefit to all

(b)(6) **01:11:49**

would be fantastic to share these plans proposals for input with vaccine developers; in what context are they being discussed?

(b)(6) **01:12:38**

I meant in what working groups for a are the discussed

(b)(6) **01:12:58**

we should take this up at next vaccine subgroup

(b)(6) **01:13:03**

How will the process herein be transmitted to the public and broader community?

(b) (6) **01:13:47**

agreed

(b) (6) **01:13:54**

What is the FDA's posture on surrogate endpoints for vaccines for SARS-CoV2 for accelerated approval?

(b) (6) **01:14:06**

Is there an overall communications strategy for this so the broader community which is proceeding on their own, have some sense of what is coming? It will influence their decision making.

(b) (6) **01:14:56**

Great progress? Will there be a way to capture status of new trial conduct given how fast COVID is advancing?

(b) (6) **01:15:17**

(b) (5) but he evidence has to be there and with some pathogens correlates can be elusive

(b) (6) **01:15:48**

Any sense of the implementation mechanism to move all of this forward?

(b) (6) **01:16:07**

congrats on the progress! i have to go to another call thanks

(b) (6) **01:18:22**

Need to run. Thanks for updates

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (WG) has fulfilled its remit and will be sunset by July 31. The status of the WG's products follows:

- The Recommendations subcommittees ("tiger teams") will continue to support the ACTIV-2 and -3 Operations Teams and will support the ACTIV-1 Operations Team when a lead network is identified.
- The playbook teams will meet on July 1. The plan is to create each playbook by mid-July. The Deloitte team will then format the playbooks in a Word template by month's end.
    - eCOA/BYOD/Hybrid: Dermot Kenny, Myron Cohen
    - eConsent: Vickey Davey, Gail Weinmann
    - Site training/tools: Teresa Takas, George Mensah
    - Remote monitoring: Lionel Bascles, Carl Garner
    - Mobile nursing: Eileen Kelly, Cindi Schmittlein, Gina Bergman, Betsy Desrosiers
- FNIH staff are seeking permanent "homes" for the playbooks and innovations spreadsheet.
- Discussions about how NIH will maintain the currency and functionality of the geotracking dashboard are ongoing.
    - Interested parties can schedule demonstrations of the dashboard with Dr. Tountas and Mr. Wachtel.
    - Individuals who are involved in ACTIV but do not have NIH credentials can request access to the dashboard by providing their name, email address, and IP address to Dr. Tountas and Mr. Wachtel. Individuals who use a VPN to access the Internet should ask their organization's IT team for the IP address range.

Appendix A: Participants List

WORKING GROUP MEMBERS

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Michelle Culp, *Office of Science Policy, NIH*

Eric Hughes, MD, PHD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer*

Stephanie James, PhD, *Senior VP of Science*

Karen H. Tountas, PhD, *Scientific Program Manager, Science*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- Dr. Tountas will work with the WG Co-Chairs to identify points of contact at the Biomedical Advanced Research and Development Authority (BARDA) and the Centers for Medicare & Medicaid Services (CMS).
- Dr. Tountas will schedule meetings for the two CTC Recommendation Committees.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive a debrief of the May 20 Executive Committee (EC) meeting, learn how the NIH *All of Us* (AoU) research program could contribute to ACTIV, and receive updates on the geotracking dashboard and composition of the CTC Recommendation Committees.

The EC will consider (1) the scope of access to the network and innovations inventories by parties outside of ACTIV and (2) expectations for longer-term sustainability of the inventories. The EC confirmed that decisions about network and resource prioritization will mostly occur at the WG level, which affirms the need to maintain strong communication with the Therapeutics-Clinical and Vaccines WGs.

AoU proposes that it could contribute to ACTIV in several ways, particularly regarding vaccine trials—such as assisting with recruitment, leveraging its healthcare provider organizations as enrollment and vaccine sites, and supporting long-term follow-up. AoU has a longitudinal study design, a diverse participant pool, and a presence in all 50 states.

The geotracking dashboard is live. WG members are encouraged to explore the dashboard and prepare feedback to be shared during a forthcoming meeting.

The members of the newly formed ACTIV-1 and -2 CTC Recommendation Committees will meet soon.

Below is a summary of the key discussion themes.

Executive Committee Meeting Update

During the May 20 EC meeting, the Co-Chairs summarized the WG's efforts to assess network capacity, compile a network inventory, identify innovations to support trials, and build a geotracking dashboard. They asked the EC to consider (1) the scope of access to the network and innovations inventories by parties outside of ACTIV and (2) expectations for longer-term sustainability of the inventories. In response to a question about prioritizing network and site resources, the EC confirmed that decisions will mostly occur at the WG level, which affirms the need to maintain strong communication with the Therapeutics-Clinical and Vaccines WGs.

Discussion

The WG discussed the importance of focused discussions with researchers leading parallel efforts and the implementers of protocols (and sponsors) to recommend networks and innovations that optimize the deployment of finite resources. Two parallel efforts within NIH are as follows:

- NIAID recently formed the COVID Prevention Network for vaccines and monoclonal antibodies, consisting of 72 sites in the United States, southern Africa, Brazil, Argentina, Peru, and Vietnam, to prepare for the launch of trials this summer.
- NHLBI is launching an adaptive clinical trial platform that integrates its networks and resources that are capable of conducting robust clinical trials of COVID-19 interventions. The Institute recently released a Research Opportunity Announcement, seeking an administrative coordinating center to manage this network of networks. NHLBI anticipates launching an inpatient trial of anticoagulants under the ACTIV banner.

Other agencies to contact are BARDA, which has established relationships with several contract research organizations (CROs), and CMS, which oversees most U.S. nursing homes. Dr. Tountas will work with the Co-Chairs to identify points of contact at BARDA and CMS.

All of Us (AoU) Program Update

AoU aims to collect and study data from at least 1 million people who reflect the diversity of the United States. It employs a longitudinal study design, collects multiple data types (e.g., electronic health records, surveys, physical measurements, biospecimens, and genomics), and treats participants as partners. To date, 271K of its 371K participants from across the country have completed its full protocol; greater than 82% are underrepresented in biomedical research and greater than 53% percent are racial/ethnic minorities. AoU has built significant infrastructure, including more than 350 clinics enrolling participants, mobile enrollment facilities, a biobank with 24-hour shipping, and a bilingual website and participant portal. AoU paused its plans to start genetic testing because of COVID-19, but its capacity includes three genome centers (genotyping and whole genome sequencing) and genetic counseling to support the responsible return of information. AoU's chief of engagement organizes the efforts of its 39 community partners (mostly national or regional).

Many AoU enrollment sites overlap with proposed ACTIV sites. AoU proposes that it could contribute to ACTIV in several ways, particularly regarding vaccine trials—such as assisting with recruitment, leveraging its healthcare provider organizations as enrollment and vaccine sites, and supporting long-term follow-up.

Dashboard Update

The dashboard is now available to WG members with NIH credentials. It should be available to all other WG members by May 23. The Deloitte team will finish loading the CRO and SMO survey data into the dashboard on May 22. WG members are encouraged to explore the dashboard and prepare feedback to be shared during a meeting to be scheduled for the week of May 25.

CTC Recommendation Committees

The composition of the committees is as follows:

- ACTIV-1: Davey, Goff, Nayak, Srinivasan
- ACTIV-2: Cohen, Davey, Payton, Resnansky

Dr. Tountas will schedule meetings for these committees.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore, PhD*, Fogarty International Center*

Badhri Srinivasan, *Head, Global Development Operations, Novartis*

Gail Weinmann, MD, *Deputy Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, *Bill & Melinda Gates Medical Research Institute*

Michelle Culp, *Office of Science Policy, NIH*

Joshua Denny, MD, MS, *Chief Executive Officer, All of Us Research Program*

Ellen Gadbois, PhD, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*

Kelly Gebo, MD, MPH, *Chief Medical and Scientific Officer, All of Us Research Program*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Dermot Kenny, *Global Head of Data Operations, Novartis*

Ashley Parker, PhD, *Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science*

Benjamin Stratton, *Senior Consultant, Deloitte*

Karen H. Tountas, PhD, *Scientific Program Manager, Science*

Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Item

Dr. Tountas will develop "cheat sheets" with high-level information about the proposed ACTIV protocols, including the agents, populations, settings, and old vs. new names.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to discuss the clinical site dashboard, the ACTIV-1 and ACTIV-2 master protocols (MPs), and plans for the Network Recommendation Committee.

WG members with NIH credentials will have access to the dashboard on May 19; WG members without NIH credentials should have access by May 22. WG members are encouraged to review the outbreak prediction models from the University of Pennsylvania and the University of Washington (at least one of which will be included in the dashboard) and to suggest enhancements to the dashboard.

The Master Protocol Sub-WG of the Therapeutics (TX)-Clinical WG seeks recommendations from the CTC WG for networks for the ACTIV-1 and ACTIV-2 protocols, which will test repurposed agents in the inpatient setting and neutralizing monoclonal antibodies in the outpatient setting, respectively.

The WG has developed a process to respond to requests from the Protocol Teams of the TX-Clinical and Vaccines WGs for network/site recommendations.

Below is a summary of the key discussion themes.

Dashboard Update

The Deloitte team discovered that a NIAID firewall was preventing downloads from the Johns Hopkins University (JHU) website, which caused performance issues. This problem was resolved by adding the JHU website to the safe list. The team is continuing data cleanup to generate a more accurate estimate of the total number of potential sites, with a primary focus on mapping sites to networks (and vice versa) and requesting network rosters. (b) (4) [redacted] Site Management Organization (SMO) data will be added to the dashboard. The team is also writing an SOP for dashboard use.

WG members with NIH credentials will have access to the dashboard on May 19; WG members without NIH credentials should have access by May 22. WG members are encouraged to review the outbreak prediction models from the University of Pennsylvania (https://penn-chime.phl.io/) and the University of Washington (http://www.healthdata.org/)—at least one of which will be included in the dashboard—and to suggest enhancements to the dashboard.

Discussion

Dr. Kurilla explained that the TX-Clinical WG and Vaccines WG will likely develop MPs or harmonize protocols with specific networks in mind. Rather than identify networks on a de novo basis, the CTC WG will identify networks that can complement or supplement the capacity of those selected by these WGs.

A WG member suggested that to ensure full coverage of hotspots, the WG should map the sites in the six high-priority networks already identified as ready to launch ACTT3 trials.

Update on ACTIV-1 and ACTIV-2 Master Protocols

The Master Protocol Sub-WG of the TX-Therapeutics WG recently met with the ACTT study team, which launched ACTT2 on May 11. The team has noticed a slower pace of recruitment and thus asked for two weeks to review its capacity to add a third protocol with three agents and 2,000 patients. To maintain the aggressive ACTIV timeline, the Sub-WG decided instead to search for another network to lead this trial (without changing the protocol). Because ACTT may not be involved in the trial, the Sub-WG renamed the ACTT3 trial ACTIV-1. Going forward, all trials will bear the ACTIV brand.

ACTIV-1

This MP will establish a Phase III confirmatory trial to test three agents (from (b)(4) b). It will employ a platform structure with independent placebo comparators for each agent. Each agent treatment arm and the shared placebo control arm will have 500 subjects. (b)(4) will be the standard of care. The placebo arm will receive an IV saline or dexterous infusion and a placebo pill.

The lead network must be highly experienced in overseeing large trials and regulatory grade data capture and monitoring. The study population will be hospitalized (moderately to severely ill), ages 18 and older, and diagnosed positive for COVID-19. Approximately 130 global sites will be needed to conduct this trial; the network must be able to launch 25% of sites within 6 weeks and 100% of sites within 6-12 weeks of receipt of protocol.

The Master Protocol Sub-WG seeks a list of recommended networks to lead this trial from the CTC WG during the week of May 25.

ACTIV-2

ACTIV-2 is a MP for testing neutralizing monoclonal antibodies in the outpatient setting. (ACTIV-3 will focus on the inpatient setting.) This MP will establish a Bayesian adaptive platform trial with seamless Phase II/III design. The NIAID ACTG network will be the lead network, but additional sites are needed. A CRO may be leveraged to link ACTG sites and other network sites.

Of the 21 monoclonal antibodies in development, 4 are expected to be ready for Phase II trials in late June or early July. Each trial arm will enroll approximately 110 patients, for a total of almost 450 patients. The network may need to scale to at least 2,000 patients if an agent progresses to Phase III. The study population is outpatient ambulatory ill, ages 18 and older, and diagnosed positive for COVID-19. Currently, the endpoints are symptomatic and virologic improvement.

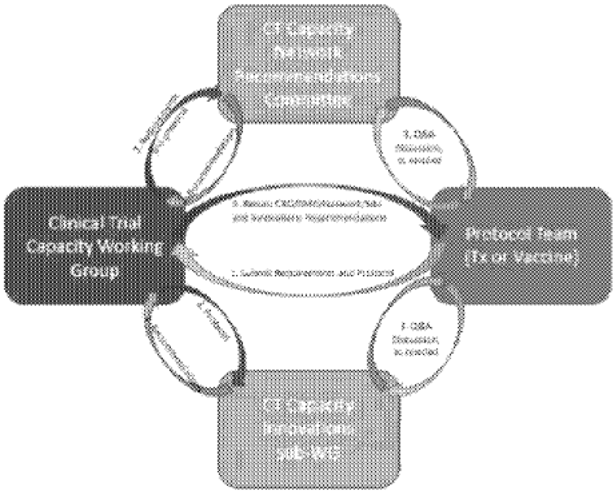
Participating networks and sites should have experience running complex adaptive trials on a global scale. The sites must have the ability to do infusions for outpatients and be willing to work with the lead network. At least 50% of sites must be able to launch within 6 weeks and 100% of sites within 6-12 weeks of receipt of protocol.

Frontier Science will lead the data coordinating efforts. However, the Master Protocol Sub-WG will explore the need to supplement data infrastructure, perhaps through additional support from Medidata.

The Leadership Group has indicated that ACTIV-2 and ACTIV-3 are the highest priority for ACTIV. The MP Sub-Working Group seeks a list of additional candidate sites for the ACTIV-2 trial from the CTC WG by May 29.

Discussion
Dr. Tountas will develop “cheat sheets” with high-level information about the proposed ACTIV protocols, including the agents, populations, settings, and old vs. new names.

Network Recommendation Committee


CT Capacity Network Recommendations Committee
Clinical Trial Capacity Working Group
Protocol Team (Tx or Vaccine)
CT Capacity Innovations Sub-WG
1. Submit Requirements and Protocol
3. Q&A Discussion, as needed
3. Q&A Discussion, as needed

Dr. Tountas reviewed the iterative process whereby the CTC WG will respond to requests from the Protocol Teams of the TX-Clinical and Vaccines WGs for network recommendations (see figure). To start the process, the Protocol Team will share the network requirements and the protocol with the CTC WG. The Protocol Team will include individuals tasked with operationalizing the trials. A CTC Network Recommendations Committee (composed of a subset of WG members to change based on the required expertise) and the Innovations Sub-WG will then interact with the Protocol Team to flesh out the necessary requirements—for not only site capacity but also innovative solutions to support the trial lifecycle. The Subcommittee and Innovations Sub-WG will submit their recommendations to the full CTC WG for review and approval before submitting a report to the Protocol Team. The report will provide details about the recommended networks, as well as highlight the pros and cons of using those networks. The WG Co-Chairs will contact WG members about participation on the Recommendations Committee.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

Carlos Garner, *PhD, Vice President, Global Regulatory Affairs, Eli Lilly and Company*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

George Mensah, MD, *Director, Center for Translation Research & Implementation Science, National Heart, Lung, and Blood Institute (NHLBI)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore, PhD, *Fogarty International Center*

Peter Stein, MD, *Director of CDER's Office of New Drugs, Food and Drug Administration*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, *Bill & Melinda Gates Medical Research Institute*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Dermot Kenny, *Global Head of Data Operations, Novartis*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

John Young, *Global Head of Infectious Disease and Vice President, Roche*

FNIH STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science*
Karen H. Tountas, PhD, *Scientific Program Manager, Science*
Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Item

- Drs. Goff and Kurilla will work together to identify the appropriate contact person in the RADx program.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to discuss the ACTIV Executive Committee meeting on May 13, the clinical site dashboard, the recent work of its sub-WGs, and the Vaccine WG presentation to the CTC WG on May 12.

The discussion of the Executive Committee focused on three main topics: (1) launching an accelerated master protocol to test all candidate SARS-CoV-2-specific monoclonal antibodies (mAbs); (2) creating and maintaining a global inventory of existing *and planned* efforts (publicly announced and not) to assess therapeutic agents for potential efficacy against COVID-19; and (3) aligning and especially communicating efforts more effectively across ACTIV partners (current and potential) and WGs. ACTIV Leadership will convene a summit of all 21 companies currently developing mAbs to gauge their willingness to submit their agents for head-to-head comparisons under an ACTIV mAb master protocol.

WG members and the Deloitte team are performing data cleanup on the dashboard, largely related to site name and location and network/site mapping. The dashboard will become available to WG members for testing during the week of May 18.

The Innovation Sub-WG has expanded the innovations inventory to include the tools and resources required for outpatient trials of therapeutics and for large-scale trials of vaccines, developed a list of technology companies that could provide those solutions, and drafted a template "RFP."

This Survey Development Sub-WG is considering ways to modify the surveys to capture information about networks' and sites' capacity to conduct clinical trials in special populations, such as the elderly, children, and pregnant women.

Below is a summary of the key discussion themes.

ACTIV Executive Committee Meeting

On May 13, the Executive Committee met with Co-Chairs of all four ACTIV WGs to discuss how ACTIV's Leadership Group might assist the WGs in fulfilling their respective remits. In particular, they discussed a letter submitted to ACTIV's Leadership Group by the Therapeutics-Clinical (TX-Clinical) WG. This letter identified challenges that have impeded the TX-Clinical WG's efforts and requested that the Leadership Group initiate specific activities to help resolve these challenges.

Meeting participants discussed three main topics: (1) launching an accelerated master protocol to test all candidate SARS-CoV-2-specific monoclonal antibodies (mAbs); (2) creating and maintaining a global inventory of existing *and planned* efforts (publicly announced and not) to assess therapeutic agents for potential efficacy against COVID-19; and (3) aligning and especially communicating efforts more effectively across ACTIV partners (current and potential) and WGs. They also considered the need to begin development of an overarching strategy to seamlessly transition from the planning phase to the execution phase of this public-private partnership.

ACTIV Leadership will convene a summit of all 21 companies currently developing mAbs for potential therapeutic efficacy against COVID-19 to gather information on their efforts and to gauge their willingness to submit their agents for head-to-head comparisons under an ACTIV mAb master protocol.

Dashboard Update

Mr. Wachtel reviewed the features of the current version of the dashboard, which provides a mechanism to query the survey data and to layer that data with Johns Hopkins University data on current COVID-19 hotspots. The Deloitte team may move the dashboard from Tableau to another platform if it cannot resolve issues with reaction time to queries.

WG members and the Deloitte team are performing data cleanup, largely related to site name and location and network-site mapping. Future surveys should include a field for site name and a standard format for reporting addresses.

A desired feature is an additional overlay with COVID-19 outbreak prediction data. The Deloitte team has identified prediction models from the University of Pennsylvania (https://penn-chime.phl.io/) and the University of Washington (http://www.healthdata.org/). However, it has discovered that a third overlay may slow performance and crowd the maps. A potential workaround is a side-by-side comparison.

The dashboard will become available to WG members for testing during the week of May 18. WG members requested the ability to list networks by size (total number of sites, rather than number of sites that completed the site survey). WG members are encouraged to provide Mr. Wachtel with additional feedback about the content and visualization features.

Discussion

The survey data in the dashboard are static; yet, the number of sites participating or planning to participate in COVID-19-related trials is constantly changing. The WG brainstormed approaches to acquiring near-real-time data about COVID-19 trial sites to maintain the dashboard's currency. Although a valuable information source, clinicaltrials.gov may not capture all trials, particularly those in the early planning stage. Dr. Stein explained that FDA is considering a process to ask sponsors of trials that have received a "Safe to Proceed" letter to report on the status of the trial and to grant permission to FDA to share the status with ACTIV.

Ms. Desrosiers added that the WG will “resurvey” candidate networks and sites about their capacity before making final recommendations.

Vaccines Working Group Debrief

The Vaccines WG has decided to adopt a model of nonidentical but harmonized efficacy trials of vaccines, with the intent to launch efficacy trials as early as July 2020. Within this model, vaccine trials will be randomized controlled trials (RCTs) of single vaccine vs. placebo and endpoint driven. Existing protocols will be harmonized to ensure comparability and standardization of the critical elements of vaccine evaluation (i.e., endpoints, common labs and DSMB, real-time data access of biostatisticians, oversight committee). Priority will first be placed on the vaccines of BARDA-funded companies, which offer a diversity of platforms and the ability to scale manufacturing.

Updates from Clinical Trial Capacity Sub-Working Groups

Innovation Sub-Working Group

The Sub-WG has expanded the innovations inventory to include the tools and resources required for outpatient trials of therapeutics and for large-scale trials of vaccines. It has developed a list of technology companies that could provide those solutions. It is drafting an “RFP” to send at a later date to gather additional information about those companies’ capabilities to support different types of clinical trials.

Dr. (b)(6) suggested that this Sub-WG connect with the National Institute of Biomedical Imaging and Bioengineering’s Rapid Acceleration of Diagnostics (RADx) fast track program, which is supporting the development and commercialization of innovative technologies to significantly increase U.S. testing capacity for SARS-CoV-2, which will be particularly useful in vaccine trials. Drs. (b)(6) will work together to identify the appropriate contact person in the RADx program.

Survey Development Sub-Working Group

This Sub-WG is considering ways to modify the surveys to capture information about networks’ and sites’ capacity to conduct clinical trials in special populations, such as the elderly, children, and pregnant women.

The Sub-WG plans to send the CRO/SMO survey to 12 SMOs on May 15. A next step is to modify the site survey to address the needs of the Vaccine WG.

Discussion

The WG discussed the recently launched NIAID trial of hydroxychloroquine and azithromycin. ACTG is executing this large, outpatient domestic trial, with a primary endpoint of hospitalization and no master protocol. WG members cautioned against using high-quality networks and sites to conduct trials that are not supported by data and/or have a low probability of benefit. Allocating resources in this way may diminish the field's capacity to conduct meaningful work in the future.

Appendix A: Participants List

WORKING GROUP MEMBERS

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Christine Sizemore, PhD*, Fogarty International Center*

Peter Stein, MD, *Director of CDER's Office of New Drugs, Food and Drug Administration*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Gail Weinmann, MD*, Deputy Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute*

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD*, Bill & Melinda Gates Medical Research Institute*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Dermot Kenny*, Global Head of Data Operations, Novartis*

Felicia Qashu, PhD*, Program Leader, Office of Strategic Coordination, National Institutes of Health*

FNIH STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Stephanie James, PhD*, Senior VP of Science*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte Consulting*

Benjamin Stratton*, Senior Consultant, Deloitte*

Karen H. Tountas, PhD, *Scientific Program Manager, Science*
Brett Tolman, *Manager, Deloitte*
Jonathan Wachtel*, Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive a report from the Vaccine WG.

The Vaccine WG has decided to adopt a model of SARS-CoV-2 vaccine development whereby "the necessary partners in the public-private partnership are based on nonidentical but harmonized efficacy trials." Within this model, vaccine trials will be randomized controlled trials (RCTs) of single vaccine vs. placebo and endpoint driven. Protocols will be harmonized to ensure comparability and standardization of the critical elements of vaccine evaluation. Priority will first be placed on the vaccines of BARDA-funded companies, which offer a diversity of platforms and the ability to scale manufacturing.

The Vaccine WG representatives identified some capacity requirements specific to vaccine trials, which will inform the ongoing efforts of the CTC WG's Survey Development and Innovations Sub-WGs.

Below is a summary of the key discussion themes.

Report from the Vaccine Working Group

Dr. Corey reported on the progress of the Vaccine WG. The WG formed a Clinical Development Sub-WG to either harmonize existing protocols or develop a master protocol (i.e., multi-arm, single placebo, comparative trial), with the intent to launch efficacy trials as early as July 2020. At least one vaccine should be available for Phase III study by that time. The overarching objective is to define and license as many vaccines as possible.

Harmonized Efficacy Trials

The Sub-WG agreed that the factors that contribute to successful comparative trials—for example, the disease is rare and localized to a specific area/entity, the parties are aligned in their Target Product Profile and goals, and the parties accept that an intermediary will hold the IND—are not operant in the COVID-19 vaccine field. Therefore, the Sub-WG decided to adopt a model for SARS-CoV-2 vaccine development whereby "the necessary partners in the public-private partnership are based on nonidentical but harmonized efficacy trials."[1]

Within this model, vaccine trials will be RCTs of single vaccine vs. placebo and endpoint driven. Protocols will be harmonized to ensure comparability and standardization of the critical elements of vaccine evaluation. Specific parameters include:

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[1] See L Corey, JR Mascola, AS Fauci, and FS Collins, "A strategic approach to COVID-19 vaccine R&D," *Science*, May 11, 2020.

- Similar protocol design, including similar definitions of the primary and main secondary endpoints
- Use of common laboratories for defining case, viral, and immunological monitoring
- Common NIAID-supported DSMB
- Access of NIAID-supported biostatisticians to each trial's data in real time so that they can perform cross-protocol analyses, especially for correlates of protection
- Governance of each individual trial by a trial oversight committee

Priority will first be placed on the vaccines of BARDA-funded companies, which offer a diversity of platforms and the ability to scale manufacturing. These platforms include traditional recombinant protein, replicating and nonreplicating viral vectors, and nucleic acid DNA and mRNA approaches. The Vaccine WG acknowledges the need to develop a structure to bring in non-BARDA-funded vaccines.

The NIAID network sites are positioned to conduct Phase III vaccine clinical trials. The network has 48 sites in the United States, 42 sites in South Africa, 55 sites in sub-Saharan Africa, and 30 sites in Mexico and South America. The investigators have been tasked with forecasting where COVID-19 outbreaks may occur. As part of this specific effort, Vaccine WG members have started to contact CEOs of meat-packing companies to ensure that sites have access to workers in factory settings, who have a high prevalence of infection.

Dr. Corey made the following comments during the Q&A/discussion:

- Trials will start with adult subjects and will hopefully reveal a correlating bridge to children. Special groups, such as the very elderly and pregnant women, may require a diversity of approaches.
- No site will conduct two ACTIV vaccine trials as the same time. However, upon closing enrollment on one trial, a site can start enrollment on a new trial.
- Trials will start sequentially rather than simultaneously, so that all trials can proceed when ready.
- Regarding the concern about immune enhancement, an advantage of a harmonized protocol is that the occurrence of grade 3 or 4 serious adverse events in a single trial will not necessitate pausing all trials.
- ACTIV will leverage the individual data systems of the sponsoring multinational companies. ACTIV will not build a centralized database and processes to collect, harmonize, and audit data.
- The WG has yet to fully consider (1) gating from Phase I to Phase III trials, (2) issues related to the durability of immune response (which translates to the length of time cohorts are followed), and (3) strategies related to high-risk populations and the healthy elderly.

Site Capacity

The Vaccine WG representatives identified the following requirements related to site capacity, which will inform the CTC WG's modification of the site survey and efforts to identify innovative solutions related to vaccine trials.

- Each site must be able to collect, store, and ship specimens.
- Each site must be able to monitor people who acquire COVID-19 on trial to assess disease severity over time. This monitoring might need to occur remotely.
- Although serological and viral load assays, which are very high throughput, will be performed by the centralized lab, on-site lab facilities will be required.

Monoclonal Antibodies

Dr. Cohen explained that the Vaccine WG is supporting both vaccines and monoclonal antibodies because they are complementary strategies. The sample size and study design of monoclonal antibodies trials will differ significantly from those of vaccine trials. Interest in studying monoclonal antibodies in the nursing home setting is increasing, in part because of hesitation to vaccinate nursing home residents, who are elderly and have multiple comorbidities. Vaccine WG members are working with several pharmaceutical companies to develop a robust research strategy to determine whether monoclonal antibodies can prevent transmission or acquisition of infection in nursing homes, where 30% of COVID-19 deaths are occurring. However, the FDA is encouraging study of antibodies as therapeutics first in severely ill hospitalized patients, then moderately ill hospitalized patients, then infected outpatients.

Updates from Clinical Trial Capacity Sub-Working Groups

During an ad hoc meeting on May 11, the WG watched a demonstration of the Tableau dashboard that will provide a mechanism to query the survey data and to layer the survey data with Johns Hopkins University data on current COVID-19 hotspots. Next steps are to identify a model that can predict COVID-19 outbreaks and then integrate that model into the dashboard.

To date, 44 networks and 521 sites have submitted surveys. The CRO/SMO survey was sent to 7 CROs last week; responses are due on May 13. The CRO/SMO survey will be sent to 13 SMOs by May 15. The next step is to modify the site survey to address the needs of the Vaccine WG.

Appendix A: Participants List

WORKING GROUP MEMBERS

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *Professor and Principal Investigator, University of Washington and HIV Vaccine*

Victoria Davey, PhD, MPH, *U.S. Department of Veterans Affairs*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, *Bill & Melinda Gates Medical Research Institute*

Ann Arvin, MD, *Professor of Pediatrics and Microbiology & Immunology, Stanford University*

Paula Annunziato, MD, *Vice President, Vaccine Clinical Development, Merck*

Paul Gillard, MD, *Senior Director, Clinical Development, GlaxoSmithKline (GSK)*

Peter Hotez, MD, PhD, *Dean for the National School of Tropical Medicine, Baylor College of*

Kathrin Jansen, PhD, *Senior Vice President, Head of Vaccine Research and Development, Pfizer*

Dermot Kenny, *Global Head of Data Operations, Novartis*

Mary Marovich, MD, *Director, Vaccine Research Program, NIAID*

Ashley Parker, PhD, *Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*

Sarah Read, MD, Deputy Director, Division of AIDS, NIAID, NIH

Merlin Robb, MD, *Chief Medical Advisor, Henry M. Jackson Foundation for the Advancement of*

Hanneke Schuitemaker, PhD, *Global Health, Viral Vaccine Discovery and Translational Medicine, Trials Network, and Past President and Director, Fred Hutchinson Cancer Research Center*
Jennifer Verani, MD, MPH, *Epidemic Intelligence Service Officer, Division of Global Health*
Mike Watson, MB ChB, MRCP, AFPM, *President, Infectious Diseases, Moderna*

FNIH STAFF
Stephanie James, PhD, *Senior VP of Science*
Michael Santos, PhD, *Associate Vice President, Science*
Benjamin Stratton, *Senior Consultant, Deloitte*
Karen H. Tountas, PhD, *Scientific Program Manager, Science*
Brett Tolman, *Manager, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*
David Wholley, MPhil, *Senior VP of Research Partnerships*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- Dr. Davey will provide Dr. Cohen with the total number of sites in the VA Community Living Centers network.
- Ms. Desrosiers and Ms. Resnansky will send a survey to their contacts at 7 CROs on May 8.
- Dr. Tountas will send the modified CRO/SMO survey to recommended SMOs during the week of May 11.
- The Clinical Trials Network Sub-WG will review the site survey to determine the need for additional questions.
- The WG will recommend SMOs for inclusion in the SMO survey (via email to Mr. Wachtel).
- Dr. Tountas will ask Dr. Janet Woodcock for the list of COVID-19 sites that she generated from ClinicalTrials.gov.

High-Level Meeting Summary

On May 6, Co-Chairs Desrosiers and Kurilla presented on the WG's progress to the ACTIV Leadership Group.

Innovation Sub-WG members (b)(5) and met with enthusiasm to participate in ACTIV and a willingness to provide services (b)(5) The Sub-WG is now focused on expanding its innovations inventory to support large-scale vaccine and prophylactic trials.

The Survey Development Sub-WG has identified 6 very promising networks and another 12 supplemental, shovel-ready networks for clinical trials of treatments. To cast a wider net, it plans to send a modified survey to CROs on May 8 and to site management organizations (SMOs) during the week of May 11. The FNIH is supporting the creation of a Tableau dashboard by Deloitte that will provide a mechanism to query the survey data and to layer the survey data with Johns Hopkins University (JHU) data on current COVID-19 hotspots.

The Clinical Trials Network Sub-WG plans to expand the inventory to include SMOs, in anticipation of the large numbers of domestic and international sites needed for prevention trials.

Below is a summary of the key discussion themes.

Report on Presentation to Leadership Group

On May 6, Co-Chairs Desrosiers and Kurilla presented on the WG's progress to the Leadership Group. During that presentation, they described the process to develop a comprehensive clinical trial capacity inventory, insights gleaned from the Network and Site Surveys, six very promising networks ("the top 6"), and the WG's timeline through May 2020.

Updates from Clinical Trial Capacity Sub-Working Groups

Innovation Sub-Working Group

For each part of the clinical trial life cycle, this Sub-WG has identified innovations/efficiencies and assessed whether each was deployed in ACTT1/2 and can be scaled to ACTT3; its transferability is contract dependent; or whether a solution is required. Sub-WG members (b)(5) capable of supporting these innovations and met with enthusiasm to participate in ACTIV and a willingness to provide services (b)(5). The Sub-WG plans to continue those discussions once the project's execution strategy and involvement of CROs become more clear. It is now focused on expanding the inventory to support large-scale vaccine and prophylactic clinical trials.

Survey Sub-Working Group

Using Network Survey responses, this Sub-WG identified 6 very promising networks (ACTG, IDCRC, INSIGHT, PCORNET, PCRC, and VA CSP) and another 12 supplemental, shovel-ready networks. Ms. Desrosiers and Ms. Resnansky plan to send a survey (modified for CROs and SMOs) to their contacts at 7 CROs on May 8.

The FNIH is supporting the creation of a Tableau dashboard by Deloitte that will provide a mechanism to query the survey data and to layer the survey data with JHU data on current COVID-19 hotspots. The FNIH will secure a Tableau license for each WG member and plans to schedule an ad hoc WG meeting on May 11 to present the dashboard.

Clinical Trial Network Inventory Sub-Working Group

This Sub-WG plans to expand the inventory to include SMOs, in anticipation of the large numbers of domestic and international sites needed for prevention trials. WG members are encouraged to recommend SMOs (via email to Mr. Wachtel). Dr. Tountas will send the modified CRO/SMO survey to the recommended SMOs during the week of May 11. She will also request a list of their sites, so that those sites can complete the Site Survey. Before then, the Sub-WG will review the site survey to determine the need for additional questions.

In addition, Dr. Tountas will ask Dr. Janet Woodcock for the list of COVID-19 sites that she generated from ClinicalTrials.gov.

General Discussion

Dr. Kurilla explained that the WG's use of "Tier 1, 2, and 3" to categorize networks has been misinterpreted as implying relative value and should therefore be avoided. Also, he acknowledged that the sum of the numbers of U.S. sites in the top 6 networks is likely a duplicated count because many sites are involved in multiple networks.

WG members stressed the importance of being able to use a hybrid clinical trial design that includes CROs and networks. Large full-service CROs are well positioned to activate and monitor sites across the country—a particular advantage given the current risk of air travel, the fast pace of the ACTIV project, and the desire to place large-scale vaccine trials in sites with forecasted outbreaks. However, the WG must assess the CROs' ability to apply standard operating procedures and tools that are not their own.

A WG member added that networks with the capacity to conduct clinical trials in skilled nursing homes—such as those of the National Institute on Aging or the Veterans Administration (VA)—may also play an important role in ACTIV. Dr. Davey will provide Dr. Cohen with the total number of sites in the VA Community Living Centers network.

WG members discussed the need for internal communication about the overarching strategy to seamlessly transition from the planning phase to the execution phase of this public-private partnership. They noted that ACTIV could also benefit from better coordination with other COVID-19 research efforts in the United States and abroad as well as from better communication about ACTIV in general.

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WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

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Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

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Stephanie James, PhD, *Senior VP of Science, FNIH*

Michael Santos, PhD, *Associate Vice President, Science, FNIH*

Elizabeth Kim, *Senior Consultant, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*
Brett Tolman, *Manager, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- Dr. Payton will share the list of the NIAID HIV/AIDS clinical trial sites that participate across multiple networks.
- FNIH staff will modify the CRO survey as described below.
- Dr. Tountas will contact Dr. Mike Santos to schedule a meeting between this WG and the Vaccine WG to begin discussions about network capacity requirements for trials of vaccines and monoclonal antibodies.
- Dr. Kenny will provide Ms. Desrosiers with a list of the technology companies contacted by the Innovation Sub-Working Group (WG).

High-Level Meeting Summary

The Clinical Trial Capacity (CTC) WG, co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive updates from the Vaccine WG and from two of the CTC-WG's three Sub-Working Groups.

The Vaccine WG has formed a Clinical Development Sub-WG to harmonize existing protocols or develop a master protocol, with the intent to launch an efficacy trial of vaccines in early July. The WG is also developing a white paper about the pros and cons of human challenge studies.

The Survey Sub-WG has received 41 responses to the Network Survey and 486 responses to the Site Survey. FNIH staff have sent a reminder email to the remaining networks. The WG reviewed the summary information from the surveys and identified questions that should be modified in future surveys. The WG also reviewed the draft CRO survey and suggested revisions and additions.

The Innovation Sub-WG discussed participation in the ACTIV project with (b)(5) and met with broad enthusiasm and a willingness to provide services (b)(5).

Below is a summary of the key discussion themes.

Update from Vaccine Working Group

Dr. Corey provided updates from the Vaccine Working Group. First, the WG has formed a Clinical Development Sub-WG to harmonize existing protocols or develop a master protocol, with the intent to launch an efficacy trial in early July. One (perhaps two) vaccines should be available for Phase III study by that time. The WG is also developing a white paper about the pros and cons of human challenge studies, which will be posted on the ACTIV website.

Dr. Cohen explained that the Vaccine WG is supporting both vaccines and monoclonal antibodies because they are complementary strategies. Monoclonal antibodies can serve as a bridge to vaccines or an option for patients who do not respond to vaccines. The WG has engaged in discussions with six pharmaceutical companies, which reported that the FDA is encouraging study of antibodies as therapeutics first in severely ill hospitalized patients, then moderately ill hospitalized patients, then infected outpatients.

The WG is working with these companies to ensure their readiness to launch prevention trials—in fact, it has already provided a Phase I option for healthy volunteers. The general consensus is that vaccine trials will be large global trials.

Updates from Clinical Trial Capacity Sub-Working Groups

Survey Sub-Working Group

Network and Site Surveys
To date, 41 networks have completed the Network Survey, and 486 sites have completed the Site Survey. Dr. Tountas sent a reminder email to the remaining networks on May 4. The WG reviewed the summary information from the Network Survey. The WG also identified questions that should be modified in future surveys, either for clarity or for tailoring to the respondent type or survey purpose:

- Network Survey Questions 10 and 11, regarding time to launch: In some cases, networks included sites that could launch in less than 6 weeks in the number of sites that could launch in 6-12 weeks.
- Network Survey Question 12, regarding standard contracts across sites: Grant-funded networks may be eliminated from consideration, because they must reply "no" to this question.
- Site Survey Question 4, regarding network name: Some sites work with more than one network, so they may be double counted.
    - Dr. Payton will share the list of the NIAID HIV/AIDS clinical trial sites that participate across multiple networks.
- Site Survey Questions 13 and 14, regarding involvement in network and non-network COVID trials: The distinction between these two questions may be unclear.
- Site Survey Questions 36-38, regarding recruitment: Respondents might report largest recruitment across clinical trials rather than a single clinical trial.
- Site Survey Question 40, regarding racial and ethnic minority groups: The minority groups will depend on the country where the site is located.

A WG member commented that, in general, the definition of "site" is unclear, providing the example of an institution with multiple sites with discrete locations, even on the same grounds, with different staff accessing slightly different populations. Is this one site?

The next step is to develop a dashboard (perhaps using Tableau or Cliq) to capture, analyze, and report the survey results. A possible add-on to this dashboard is a tool that geo-tracks the number of COVID-19 cases reported within the past 2 weeks, informed by county-level data from Johns Hopkins University.

CRO Survey

The WG reviewed the draft CRO survey, which will be released this week, and suggested the following changes and additions:

- After Question 7, add a question with a text field so that respondents can describe the "other" types of studies they are conducting.
- For Question 10, add contact information so that CROs can share their heat maps.
- For Questions 13 and 14, change "network" to "CRO."
- Add a question about experience conducting studies with mixed models.
- Add a question about experience working with federal government contracts.
- Add a question about innovations used in the infected outpatient setting and the prophylactic setting.

General Discussion

The WG Co-Chairs reiterated that the current surveys reflect the ACTIV project's prioritization of patient populations: they were designed to access networks' capacity to launch clinical trials of repurposed compounds in moderately and severely ill hospitalized patients. The Sub-WG will modify the existing surveys—or develop new surveys—as the focus shifts to the outpatient/ambulatory ill and unaffected (i.e., prophylaxis) populations. Dr. Tountas will contact Dr. Mike Santos to schedule a meeting between this WG and the Vaccine WG to begin discussions about network capacity requirements for trials of vaccines and monoclonal antibodies.

Innovation Sub-Working Group

Sub-WG members have (b)(5) the ACTIV project. They met with broad enthusiasm and a willingness to provide services (b)(5). Kenny will provide Ms. Desrosiers with a list of the technology companies contacted by this Sub-WG.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

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James Doroshow, MD, *Director of the Division of Cancer Treatment and Diagnosis, National Cancer Institute*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases (NIAID)*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Felicia Qashu, PhD, *Program Leader, Office of Strategic Coordination, National Institutes of Health*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

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Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Dermot Kenny, *Global Head of Data Operations, Novartis*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science, FNIH*
Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*
Michael Santos, PhD, *Associate Vice President, Science, FNIH*
Elizabeth Kim, *Senior Consultant, Deloitte*
Benjamin Stratton*, Senior Consultant, Deloitte*
Jonathan Wachtel*, Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- Dr. Goff will provide Dr. Adam with the PEDAL and SIREN master protocols (MPs).
- Dr. Davey will provide Dr. Adam with contact information for someone who can speak to the Therapeutics-Clinical WG about the VA Health Care System MP.
- Dr. Nayak will share a list of questions that her team considered problematic while completing the survey.
- Dr. Tountas will share the WG's suggestions about external communication with the Leadership Group.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Elizabeth Desrosiers and Michael Kurilla, convened to receive updates from its three Sub-Working Groups.

The Survey Sub-WG has received 34 responses to the Network Survey. It used a five-part filter to identify 13 networks as potential Tier 1 candidates. Next steps are to perform a sensitivity analysis of the survey results and to more fully vet these 13 networks.

The Clinical Trial Network Inventory Sub-WG plans to expand the inventory to include CROs and is revising the survey instrument to capture the information needed to determine a CRO's capacity.

For each part of the clinical trial life cycle, the Innovation Sub-WG has identified an innovation and assessed whether it was deployed in ACTT1/2 and can be scaled to ACTT3; its transferability is contract dependent; or a solution is required. The Sub-WG is in preliminary discussions with technology companies that have expressed an interest in contributing to the project.

Below is a summary of the key discussion themes.

Update from Survey Sub-Working Group

The WG has received 34 responses to the Network Survey. MS Forms is limited in terms of how summary data are presented. Therefore, the Sub-WG will meet on May 3 to discuss creation of a dashboard to facilitate analysis of survey results. It will also discuss gaps in the survey question bank and survey questions that may be misinterpreted or difficult to answer. During that meeting, Dr. Nayak will share a list of questions that her team considered problematic while completing the survey. Further, Dr. Cohen agreed to share surveys seeking very granular information that Fred Hutch has sent to its networks, on the condition that they are considered confidential.

The purpose of the current survey is to identify Tier 1 networks to launch ACTIV trials of repurposed agents. Future surveys will be tailored to assess the capacity of networks to conduct trials of vaccines and monoclonal antibodies. The Survey Sub-WG applied five filters to the network responses to generate a subset of candidates.

1. At least 50% of the network's sites can launch an ACTIV trial within 1.5 months of protocol receipt, or at least 80% can launch within 3 months.
2. Contracts across sites are standardized.
3. Sites will accept a flat fee for participant visits.
4. The network has experience with a central IRB.
5. The network has experience with research and care of patients with COVID-19.

These filters identified 11 networks: PETAL, AIDS Clinical Trials Group, Palliative Care Research Cooperative, INSIGHT, Antibacterial Resistance Leadership Group, Department of Veterans Affairs Cooperative Studies Program, REPRIEVE, Cardiothoracic Surgical Trials, PrecISE, IMPACT, and the Nephrotic Syndrome Study. If the last filter is loosened, the Consortium for Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer and the Heart Failure Network can be added to the list.

The next steps are to perform a sensitivity analysis to understand why networks (including some expected networks) did not make the list and to more fully vet those that did.

Approximately one-quarter to one-third of networks indicated the need for assistance with accessing PPE, swabs, and viral transport media. The WG agreed that a follow-up question should also address testing equipment and reimbursement.

Finally, the average time to respond to the survey is 234 minutes. WG members agreed that respondents should receive a "thank you" email.

Update from Clinical Trial Network Inventory Sub-Working Group

The Sub-WG plans to expand the inventory to include CROs, because the major full-service CROs are already significantly involved in COVID-19 research and have extensive investigator databases. The Sub-WG is revising the survey instrument to capture the information needed to determine a CRO's capacity. Questions include the number of current and planned COVID-19 trials, trial phase, geographic locations, type of product or mechanism of action, experience with prevention and therapeutic research, and sponsor companies. The WG agreed that understanding CROs' roles in hybrid studies is also important.

The Sub-WG also decided to generate a heat map of sites that are enrolling or plan to enroll patients, using clinicaltrials.gov and the survey results as sources.

Participants briefly discussed the administrative considerations for CROs in ACTIV trials, for example, the need for a PI who is responsible for the clinical aspects of the work and an entity that holds the contract and serves as a point of contact. A WG member suggested adding a question to the Network Survey about experience working with and overseeing CROs.

Innovation

This sub-WG continues to revise the inventory of innovations that will be required throughout the life cycles of ACTIV trials, both under the ACTT3 protocol and the de novo MP. For each part of the life cycle (planning, start-up, enrollment/treatment, closeout and reporting), the sub-WG identified an innovation and assessed whether (1) it was deployed in ACTT1/2 and can be scaled to ACTT3; (2) its transferability is contract dependent (bespoke or proprietary products may not be transferrable to external vendors); or (3) a solution is required. The Sub-WG used color coding in the inventory matrix for these designations, accompanied by explanatory notes (e.g., vendor, training needs). The Sub-WG is in preliminary discussions with technology companies that have expressed an interest in contributing to the project.

WG members discussed the need for innovative approaches to establishing and managing a network of networks and to "bolting onto" and linking to existing MPs.

General Discussion

Ms. Desrosiers explained that the Therapeutics-Clinical WG is researching other groups with existing MPs that ACTIV can "bolt onto" rather than develop a de novo MP. WG members suggested that the Therapeutics-Clinical WG consider the PETAL MP for hospitalized patients, the SIREN MP for outpatients, and the VA Healthcare System MP for hospitalized patients (under development).

- Dr. Goff will provide Dr. Adam with the PEDAL and SIREN MPs.
- Dr. Davey will provide Dr. Adam with contact information for someone who can speak to the T-C WG about the VA MP.

WG members expressed (b)(5) [redacted] in the same population. Some WG members suggested that FNIH could (b)(5) [redacted]. Dr. (b)(6) [redacted] will share this suggestion with the Leadership Group.

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WORKING GROUP MEMBERS

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Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Ashley Parker, PhD, *Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*

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Stacey Adam, PhD, *Director, Cancer, Research Partnerships, Foundation for the NIH (FNIH)*

Stephanie James, PhD, *Senior VP of Science, FNIH*

Karen H. Tountas, PhD, *Scientific Program Manager, Science, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Marie Alvarez, *Consultant, Deloitte*

Margaret Anderson, *Managing Director, Deloitte*

Benjamin Stratton, *Senior Consultant, Deloitte*

Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- WG members will direct PIs who want to suggest candidate agents (and also forward their emails) to Rachel Pollock at (b) (6).
- Mr. Wachtel will resend an email dated April 23 to the WG dated April 23, in which he requested contact information for the DoD PLC, Kaiser, GAP-Net, Cleveland Clinic, and University of Oxford networks.
- Dr. Garner will forward the network information from Lilly's Global Clinical Operations Team to the Inventory Sub-Working Group (Sub-WG).
- Dr. Payton will contact Dr. Clinton Wright (NINDS) to collect information about Strokenet.

High-Level Meeting Summary

The Clinical Trial Capacity Working Group (CTC WG), co-chaired by Drs. Elizabeth Desrosiers and Michael Kurilla, convened to receive updates from the Agent Prioritization Sub-WG of the Therapeutics-Clinical WG and from its own three Sub-WGs. The Agent Prioritization Sub-WG has developed a four-step process to prioritize candidate agents for ACTIV clinical trials. The Inventory Sub-WG has identified 59 networks for potential inclusion in ACTIV trials; the Survey Sub-WG plans to release the two surveys today; and the Innovation Sub-WG has populated a matrix of innovations to be deployed throughout ACTIV trials—highlighting those that are "must-haves" for ACTT3 trials.

Below is a summary of the key discussion themes.

Presentation by Agent Prioritization Sub-WG of the Therapeutics-Clinical WG

The Therapeutics-Clinical WG is developing a list of candidate agents based on the following sources: R&D Prioritization, UK Prioritization, Milken Database, BioCentury Database, NIH Publication Database, bioRx Database, and PI submissions.

Its Agent Prioritization Sub-WG has developed a four-step process to prioritize the agents for ACTIV clinical trials. First, agents will be organized into three categories (or "waves"): antivirals, host-target/immune modulators, and symptomatic/supportive therapy (e.g., anticoagulants).

Second, each agent will undergo a rapid triage by a small team of experts (including those from other WGs as needed). The triage applies five screening tests, all of which must be passed for potential agents to move to the next review phase. The tests are (1) Is the agent IND-enabled and FDA-approved? (2) Is there clinical or preclinical evidence that the agent may treat COVID-19? (3) Is the agent already being tested in robust clinical trials? (4) Is the MOA relevant to COVID-19 and are other agents with the same MOA being tested? and (5) Is the agent suitable for populations prioritized by ACTIV?

Third, the agents that pass triage will be reviewed against the major criteria of therapy type, clinical development stage, clinical evidence, MOA, and patient population. Finally, the top candidates will be assessed against logistics benchmarks. To supplement the expert gestalt, the Sub-WG envisions application of a scoring system to provide unbiased quantitative assessments.

Based on the ACTT sites' current capacity, the Sub-WG expects that the top 2-3 agents will enter ACTIV clinical trials.

The NIH Office of the Director is maintaining a list of agents suggested by external PIs and groups. These agents will be added to the master list and reviewed when appropriate and in a systematic way. WG members should direct interested parties (and also forward their emails) to Rachel Pollock at (b) (6).

Updates from CTC WG Sub-Working Groups

Clinical Trial Network Inventory

Through internal brainstorming sessions, a survey of NIH colleagues, and coordination with the NIH Office of the Director (OD), the Sub-WG has now identified 59 clinical trial networks. Based on the upcoming survey results, the networks will be organized into three tiers:

- Tier 1: Full-service network with currently operational clinical research sites (at least 5-10) and infrastructure. Ability to initiate a trial at 50 percent of its sites to begin enrollment within 6 weeks of receiving the protocol.
- Tier 2: Network with incomplete infrastructure that will require 6-12 weeks to begin enrollment.
- Tier 3: Organization with capability to implement clinical trials but lacking some infrastructure components. Will require more than 12 weeks to begin enrollment.

Six networks have been identified as high-priority because they are already conducting or can immediately launch COViD-19 trials.

The following action items emerged from the WG discussion:

- Mr. Wachtel will resend an email dated April 23 to the WG, in which he requested contact information for the DoD PLC, Kaiser, GAP-Net, Cleveland Clinic, and University of Oxford networks.
- Dr. Garner will forward the network information from Lilly's Global Clinical Operations Team to the Inventory Sub-WG today.
- Dr. Payton will contact Dr. Clinton Wright (NINDS) to collect information about Strokenet.

Survey Development

The Sub-Group has developed two surveys, one for network Clinical Coordinating Centers (CCCs) or Data Coordinating Centers (DCCs) and one for individual sites. The network-level survey will include questions such as number of sites; locations; time to launch; standard contractual arrangements; need for PPE and equipment; ability and willingness to be subject to a central DSMB/DMC; ongoing or planned COVID-related research; experience with central IRBs, e-consent, and adaptive study design; ability to recruit and manage priority patient populations; and existence and expertise of a coordinating center, data coordinating center, drug distribution center, and imaging reading center.

The site-level survey is designed to assess constraints on capacity due to ongoing or planned COVID-related research; expertise with e-consent and telemedicine; number of dedicated staff; ability to follow patients into the ICU; demographics of the patient populations served; and standard of care for COVID patients.

The surveys and accompanying message from Dr. Collins will likely be sent today, with responses tentatively due by April 27 (network) and April 29 (site).

Innovation

This sub-WG has developed an inventory of innovations or activities that will be required throughout the life cycles of ACTIV trials, both under the ACTT3 protocol and the de novo master protocol. For each part of the life cycle (planning, start-up, enrollment, treatment, closeout/reporting), the sub-WG identified an innovation and assessed whether it is:

- a must-have for ACTT3;
- a process, technology, or service;
- required for outpatient/decentralized trials;
- applicable to the in-hospital setting;
- an ACTT-1 deployed solution; and
- already delivered by (or capable of being delivered by) certain vendors.

Dr. Srinivasan walked the WG through an “Inventory of Innovations” matrix, which captures these elements and has been populated by the sub-WG.

Participants noted that these innovations and activities are currently being deployed in experienced networks and are subject to FDA guidance. Additional opportunities for innovation will likely arise as trials move outside of the hospital setting.

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Ashley Parker, PhD, *Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH*
John Young, *Global Head of Infectious Disease and Vice President, Roche*

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Brett Tolman, *Manager, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Action Items

- Mr. Wachtel and Dr. Goff will finalize the network-level survey questions.
- Dr. Desrosiers and Mr. Wachtel will create and test each survey in MS forms by COB April 23.
- Dr. Desrosiers will draft an introductory message from Dr. Collins for each survey.
- Dr. Nayak will provide the WG with a synopsis of the ACTT protocol.

High-Level Meeting Summary

The Clinical Trial Capacity Workgroup (CTC WG), co-chaired by Drs. Elizabeth Desrosiers and Michael Kurilla, convened to receive updates from the Master Protocol (MP) Sub-Working Group (Sub-WG) of the Therapeutics-Clinical WG and from its own three Sub-WGs. The MP Sub-WG is moving forward with a repurposed MP for immediate trials and a de novo MP for the longer term. The Inventory Sub-WG has identified 38 networks for potential inclusion in ACTIV trials, the Survey Sub-WG has developed two survey instruments to assess those networks' capabilities and capacities, and the Innovation Sub-WG has developed a matrix to guide deployment of innovative solutions throughout the trial life cycle.

Below is a summary of the key discussion themes.

Presentation by Master Protocol Sub-Working Group

The MP Sub-WG has prioritized patients populations to be addressed with existing MPs or a de novo MP in the following order: (1) hospitalized/moderately ill and critically ill/ventilated, (2) outpatient/ambulatory ill, and (3) prophylaxis/prevention. The Sub-WG acknowledges that the difference between moderately ill and critically ill patients, which can become quickly blurred and varies by site, must be carefully considered.

To meet its stated objective to rapidly initiate clinical trials of repurposed compounds with Priority Population 1, the Sub-WG will amend the protocol of an existing study (most likely ACTT II). The intent is to use that study's sites (perhaps with supplements) and Data Monitoring Committee (DMC)/Data Safety Monitoring Board (DSMB). The timeline for this work is 30-35 days.

For studies of Priority Populations 2 and 3, the Sub-WG will develop a de novo MP ("the gold standard") that is fully adaptive to any patient population or setting and to Phase III or II clinical trials). This de novo MP will call for a central DMC and IRB that span networks (in a "network of networks"), which will be challenging to establish but necessary for coordination. The timeline for this work is 50-80 days. The MP Sub-WG will solicit this WG's input regarding the MP design.

Regarding trials with Priority Population 3, the MP Sub-WG will focus on trials of monoclonal antibodies (versus vaccines, which are the purview of the Vaccines WG), which may require modification of the aforementioned de novo MP or development of another unique MP.

Updates from CTC WG Sub-Working Groups

Clinical Trials Network Sub-Working Group

The Sub-WG has defined a network as one with a Leadership and Operations Center to provide scientific and administrative leadership, central operations, and communications; a Statistical and Data Management Center to provide biostatistical leadership and centralized data management; a Laboratory Center to provide laboratory services necessary to conduct clinical research; and a portfolio of Clinical Research Sites where participants are screened and enrolled.

The Sub-WG has focused on networks with access to adult populations and with domestic reach. It has organized networks in three tiers:

- Tier 1: Full-service network with currently operational clinical research sites (at least 5-10) and infrastructure. Ability to initiate a trial at 50 percent of its sites. Can begin enrollment within 6 weeks of receiving the protocol.
- Tier 2: Network with incomplete infrastructure that will require 6-12 weeks to begin enrollment.
- Tier 3: Organization with capability to implement clinical trials but lacking some infrastructure components. Will require more than 12 weeks to begin enrollment.

The Sub-WG asked their colleagues in NIH Institutes and Centers (e.g., NIAID, NHLBI, NCATS, NIA, NIDDK) to identify known robust networks. It then divided the resulting 38 networks into three groups: NIH Institutes and Centers, academic research organizations, and other institutions. Finally, it identified 6 high-priority networks that are ready to launch: ACTG, HPTN, HVTN, PEDAL, DCRI, and TIMI. Sub-WG members will contact these networks to gauge their interest in participating in ACTIV in order to build an advance pool of high-capacity trial sites.

Survey Development

The Sub-Group has developed two surveys, one to send to network Clinical Coordinating Centers (CCCs) or Data Coordinating Centers (DCCs) and one to send to individual sites. The intent is to ask each CCC/DCC to forward the site-level survey to the individual sites to facilitate engagement and data collection.

The network-level survey will include questions such as number of clinic sites; locations; time to launch; standard contractual arrangements; need for PPE and equipment; ability and willingness to be subject to a central DSMB/DMC; ongoing or planned COVID-related research; experience with central IRBs, e-consent, and adaptive study design; ability to recruit and manage priority patient populations; and existence and expertise of a coordinating center, data coordinating center, drug distribution center, and imaging reading center.

The clinic-level survey is designed to assess constraints on capacity due to ongoing or planned COVID-related research; expertise with e-consent and telemedicine; number of dedicated staff; ability to follow patients into the ICU; demographics of the patient populations served; and standard of care for COVID patients.

The Sub-WG will create and test both surveys in MS forms by COB April 23. Each will include a message from Dr. Francis Collins and a link to the ACTIV press release.

Innovation Sub-Working Group

The objectives of this Sub-WG are to create an agile, efficient clinical trial execution model using the latest innovations. The scope of the model includes trial design, site selection, patient enrollment, trial operations, trial monitoring, and closeout and reporting. Innovations will be deployed in stages, starting with those that can be used immediately and then moving to address additional needed infrastructure, third parties, and informatics. As a starting point, the Sub-WG will fill in its solutions/deployment matrix based on the ACTT II protocol.

Funding and Contract Structures and Processes

The WG agreed on the need to establish streamlined funding and contract structures and processes, and to engage personnel sophisticated in this effort, to ensure that the launches of clinical trials are not delayed by logistical considerations.

Appendix A: Participants List

WORKING GROUP MEMBERS

Lionel Bascles, PhD, *Senior VP, Global Head of Clinical Sciences & Operations, Sanofi*

Myron Cohen, MD, *Associate Vice Chancellor for Global Health and Medical Affairs, Director, Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill*

Larry Corey, MD, *President and Director Emeritus, Fred Hutch*

Elizabeth Desrosiers (Co-Chair), MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

James Dickens, *Program Manager, National Center for Advancing Translational Sciences*

James Doroshow, MD*, Director of the Division of Cancer Treatment and Diagnosis, National Cancer Institute*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute*

Michael Kurilla (Co-Chair), MD, PhD, *Director – Division of Clinical Innovation, National Center for Advancing Translational Sciences (NCATS)*

Seema Nayak, MD, *Director, Office of Clinical Research Resources, National Institute of Allergy and Infectious Diseases*

Manizhe Payton, *Director, Office of Clinical Site Oversight, National Institute of Allergy and Infectious Diseases*

Laura Resnansky, *Vice President, Global Head of Clinical Operations – Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Genentech*

Badhri Srinivasan, *Head, Global Development Operations, Novartis*

Peter Stein, MD, *Director of CDER's Office of New Drugs, Food and Drug Administration*

Michael Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

Janet Woodcock, MD, *Director of the Center for Drug Evaluation and Research, Food and Drug Administration*

INVITED PARTICIPANTS

Jintanat Ananworanich, MD, PhD, *Bill & Melinda Gates Medical Research Institute*

Christine Colvis, PhD*, Director, Drug Development Partnership Programs, NCATS*

Penny Heaton, MD, *Chief Executive Officer, Bill & Melinda Gates Medical Research Institute*

Eric Hughes, MD, PHD*, Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis*

Ashley Parker, PhD*, Special Assistant to Acting Chief of Staff to the NIH Director, National Institutes of Health*

Laura Resnansky, *Vice President, Global Head of Clinical Operations - Immunology, Infectious Diseases, Ophthalmology and Neuroscience, Roche/Genentech*

John Young, *Global Head of Infectious Disease and Vice President, Roche*

FNIH STAFF

Stacey Adam, PhD, *Director, Cancer, Research Partnerships, Foundation for the NIH (FNIH)*
Stephanie James, PhD, *Senior VP of Science, FNIH*

Karen H. Tountas, PhD, *Scientific Program Manager, Science, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rose Marie Alvarez, *Consultant, Deloitte*
Nina Gonzalez, *Senior Manager, Deloitte*
Elizabeth Kim, *Senior Consultant, Deloitte*
Benjamin Stratton, *Senior Consultant, Deloitte*
Brett Tolman, *Manager, Deloitte*
Jonathan Wachtel, *Manager, Deloitte*

Nancy Tuvesson, MBA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From (b)(6) to Everybody 00:26:11

Can someone clarify whether there is a separate protocol envisioned for the outpatient setting? If so, is that a backburner activity, or are there capacity issues we should considering for that effort?

From (b)(6) to Everybody 00:41:56

The impact of early therapy on reducing hospitalization if successful is high, hence backburning them seems unwise. Having said that the infrastructure to conduct them may be more scarce at the moment.

From Myron Cohen to Everybody 00:57:28

There are far more outpatients than in patients.

High-Level Meeting Summary

The ACTIV-2/-3 Trial Oversight Committee (TOC) met to discuss ACTIV-2 and ACTIV-3 updates, (b) (4) manuscript authorship and acknowledgement guidelines, and the Communications Standard Operating Procedure (SOP).

Trial Status Updates

ACTIV-2

ACTIV-2 has enrolled (b) (4) and activated 59 sites as of November 4. The ACTIV-2 team noted that the demographics of the enrolled patient population are improving to become more representative of the general population and this improvement will hopefully continue through the use of ACTIV-2 outreach strategies. The team is developing the second version of the ACTIV-2 master protocol, which will include the (b) (4) agent.

The ACTIV DSMB has approved ACTIV-2 to advance the (b) (4) agent into a Phase III clinical trial; the DSMB considered all available clinical data generated thus far on the agent, including (b) (4) clinical trial data, when making this decision. The trial team h(b) (4).

Discussion

Dr. (b) (6), (b) (4) requested feedback from the TOC regarding whether to advance (b) (4) into ACTIV-2. This agent was recommended for advancement by the Therapeutics-Clinical Working Group's (TX-Clinical WG's) Agent Prioritization Subgroup (APSG); however, the data package provided to the APSG did not include animal data or clinical data against SARS-CoV-2. (b) (4) is involved in several ongoing small clinical trials, but the data from these trials are not yet available. Dr. (b) (6), (b) (4) recommended that this agent be advanced into Phase II studies in order to generate missing clinical data against SARS-CoV-2. The TOC agreed with this recommendation and endorsed advancing (b) (4) into ACTIV-2.

ACTIV-3

ACTIV-3 continues to pause patient enrollment and site activation after meeting with the DSMB on October 26.

The ACTIV-3 team will submit the second version of its master protocol to the FDA on November 5 and is currently incorporating NIAID regulatory review comments into the document; this version will include the (b) (4) The third version of the master protocol will likely include agents from (b) (4) (pending Agent Selection Committee [ASC] review). (b) (4) in the same patient population as ACTIV-3, but has recently paused patient enrollment for (b) (4) DSMB to evaluate all available safety data to assess whether to continue the clinical trial. The ACTIV-3 team will meet with (b) (4) on November 6 to discuss updates on the (b) (4).

Dr. (b)(6) is leading the development of a manuscript that will detail findings from the ACTIV-3 trial with the (b)(4) and recent DSMB considerations.

Discussion

Presentation of (b)(4)

Participants agreed that the TOC would benefit from a presentation on the ACTIV-3 (b)(4), as well as descriptions of the findings from the recent DSMB review. Dr. (b)(6) will present to the TOC during its next meeting using materials generated thus far for the ACTIV-3 manuscript.

Efficacy of Agent Classes

Participants discussed how the results of the (b)(4) may affect other ACTIV trials of similar antibody-based therapeutics. Dr. (b)(6) noted that the (b)(4) does not appear to have a significant effect on patient outcomes and that plasma therapies are also proving ineffective. Participants emphasized that antibodies may need to be administered as early as possible to impart the desired effects and that the data from (b)(4) will provide more clarification on whether the timing of administration requires reevaluation. Drs. (b)(6) noted that (b)(4) continues to withhold data from its ongoing clinical trials and has not been forthcoming with details related to its pause in patient enrollment; however, (b)(4) may unblind its data if its clinical trial is permanently stopped.

Dr. (b)(6) recommended updating the ACTIV-3 master protocol to better suit additional compound types, specifically immune modulators, in the event that antivirals are ineffective against COVID-19. Participants agreed to discuss this topic during the next TOC meeting.

Agent Advancement in ACTIV-3

Participants discussed whether to advance additional agents into ACTIV-3 after the (b)(4) trials are launched or instead to wait until trial results from the already committed agents (i.e., (b)(4)) can be reviewed and evaluated. ACTIV-3 leadership will discuss this topic during their November 7 meeting. Dr. (b)(6) emphasized that applicant companies must be notified as quickly as possible if their agents will not be advanced into an ACTIV clinical trial. For example, (b)(4) have each applied to participate in both ACTIV-2 and -3; (b)(4) agent is an nAb, whereas (b)(4)' agent is not.

Participants decided to halt advancement of any new nAbs into ACTIV-3 until the committed nAbs demonstrate significant benefit within the inpatient population. Dr. (b)(6) will contact (b)(4) to share that ACTIV-2/-3 are pausing new agent advancement and to recommend that it pursue other funding opportunities. However, participants agreed to pursue the (b)(4) agent because of its unique mechanism of action. Drs. (b)(6) (b)(6) will contact Dr. (b)(6) to discuss signing CDAs in order to accelerate the receipt of recent preclinical data on the (b)(4) agent. Dr. (b)(6) will share with the TOC notes on the ASC's review of the (b)(4) agent.

Dr. (b) (6) offered to share with the TOC any unique or promising antibodies that are identified by the (b) (4)

Topics for Discussion

(b) (4) Response to ACTIV-2's Desire to Publish Results

Dr. (b) (6) noted that (b) (4) does not want ACTIV-2 to release data generated using the (b) (4) agent. (b) (4) is concerned that data generated on a small cohort ((b) (4) impact whether the agent is approved for Emergency Use Authorization (EUA). The ACTIV-2 team aims to publish these results to evaluate correlations between viral load and observed symptoms in order to further understand how COVID-19 trials must be designed.

Participants agreed that (b) (4) cannot prevent the public release of these data indefinitely because they were generated with funding from the U.S. Government. However, participants agreed that respecting the wishes of another institution is also important. The ACTIV-2 team will review its CTA (b) (4) and follow the procedures outlined related to releasing data.

Dr. (b) (6) recommended convening the ACTIV-2 team and (b) (4) (either all data or a small unblinded subset of patients) and discuss the company's concerns related to the release of these analyses and data. Participants agreed with this recommendation. Dr. (b) (6) will contact (b) (4) lly to discuss performing joint analyses of the ACTIV-2 (b) (4)

Manuscript Authorship and Acknowledgements

Participants discussed the acknowledgement requirements for ACTIV-2 and -3 manuscripts. The ACTIV-2 team aims to follow the AIDS Clinical Trials Group's (ACTG's) authorship rules, which Dr. (b) (6) r will share with the TOC; the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) is already familiar with these authorship rules. ACTIV-3 has developed an authorship protocol that would acknowledge the ACTIV-3 team within the authors list and include a list of all individuals within that team within the acknowledgements section; all other contributing groups, such as Operation Warp Speed, will be acknowledged in the same manner.

Participants agreed that authorship requirements should lean towards inclusion, rather than exclusion, in order to adequately acknowledge all personnel helping facilitate ACTIV-2 and -3.

Dr. (b) (6) noted that the TX-Clinical WG will name WG Co-Chairs and writing team members as authors on its manuscripts and to include the entire TX-Clinical WG in the acknowledgements.

Proposed Communications Standard Operating Procedure

(b) (4) d. Dr. (b) (6) invited TOC members to review the SOP and share feedback. Once feedback is received, Dr. (b) (6) will share the updated communications SOP with ACTIV leadership and the Cross-Trial leadership group. (b) (4) relates only to ACTIV-2 and -3; however, participants recommended that the (b) (4)

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles*

Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID, NIH*

David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI), NIH*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID, NIH*

James P. Kiley, PhD, *Director, Division of Lung Diseases, NHLBI, NIH*

Peter Kim, MD, *Director, Therapeutics Research Program, Division of AIDS (DAIDS), NIAID, NIH*

H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID, NIH*

Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*

Gilbert "Lynn" Marks, MD, *Senior Adviser to BARDA, Office of the Director*

James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota and Principal Investigator, INSIGHT*

Sarah Read, MD, *Deputy Director, DAIDS, NIAID, NIH (WG Co-chair)*

Erica Ollmann Saphire, PhD, *Professor, La Jolla Institute for Immunology*

David (Davey) Smith, MD, *Professor of Medicine, University of California, San Diego*

OTHER INVITED ATTENDEES

Kevin Bugin, PhD, *Director of Special Programs Staff, Office of New Drugs, Food and Drug Administration*

William Erhardt, MD, *Clinical Advisor to ACTIV-2 and Chief Executive Officer, Soundview Pharmaceutical Consultants*

Rachel Harrigan, *Clinical Consultant for Drug Development and Former Head of Development Operations, Pfizer*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Nada Saleh, MS, *Clinical Trials Specialist, Social and Scientific Systems Inc.*

STAFF

Stacey Adam, PhD, *Director, Cancer, Foundation for the NIH (FNIH)*

David Wholley, MPhil, *Senior Vice President of Research Partnerships, FNIH*

Evan Appell, *Consultant, Deloitte*

Helen Q. Chen, *Consultant, Deloitte*

Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From (b)(6) to Everyone: 03:12 PM
How does an agent get a 2.67 out of 2 for Availability?

From (b)(6) to Everyone: 03:13 PM
Is there an interest in animal model data? A quick mouse study did not look promising (needs repeating). And there is ongoing work in (b)(4)

From (b)(6) (he/his) to Everyone: 03:16 PM
Ann, if you have those camostat data, could you send them to me at (b)(6) ?

From (b)(6) Everyone: 03:28 PM
I think you cannot hear me. Certainly AZ is counting on ACTIV 3 at this point.
Regarding (b)(4) they have not unblinded themselves yet.

From (b)(6) to Everyone: 03:40 PM
I think that we should really want this
Impressed that Cliff has the stomach to bring up politics

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed scenario planning for the WG's future and received Subgroup updates. Dr. Joseph Menetski noted that contents of agent prioritization discussions and DSMB reviews appear to have been publicly disclosed on several recent occasions and reminded WG members that ACTIV conversations are confidential. Dr. John Young will deliver this reminder at upcoming agent prioritization meetings.

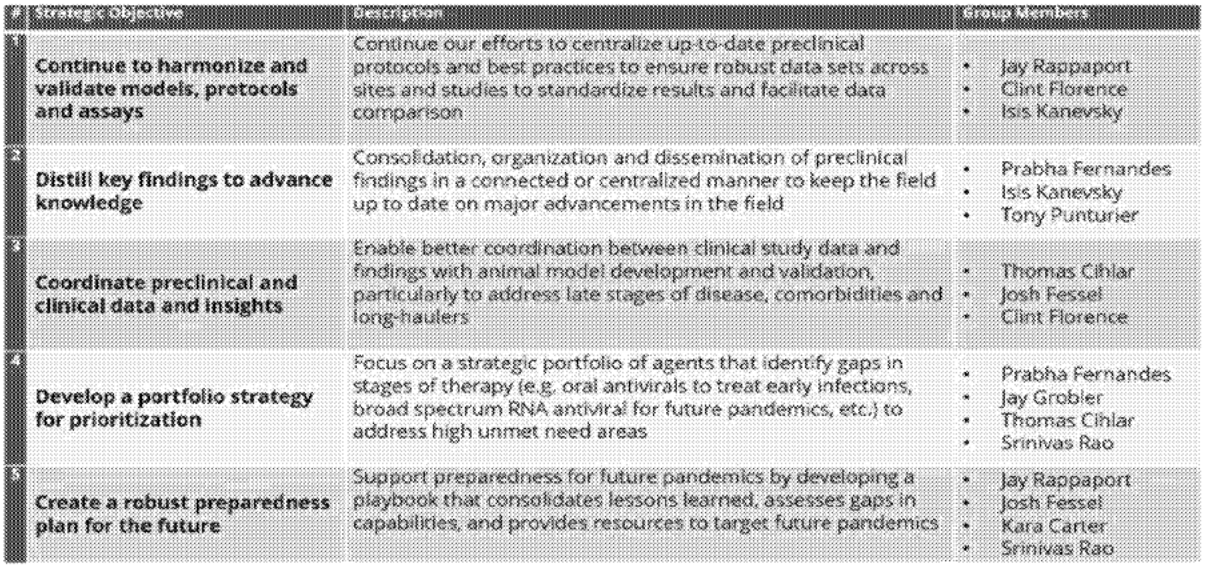
Action Items

- Dr. Prabha will share with the WG parts of the HSPD-21 (National Strategy for Public Health and Medical Preparedness) that are currently under development
- Dr. Sarah Connelly and Mr. Harrison Hawk will schedule short meetings starting this Friday 10/16 for the strategic objective subgroups to work together to populate the pre-populated forms. The WG aims to present a set of five completed objectives to the Executive Committee at its next meeting in early November.

Scenario Planning Exercise

During its last two meetings, the Preclinical WG has begun a scenario planning exercise that seeks to define the most important COVID-19 and broader pandemic-related preclinical research activities for 2021 and beyond. Its recommendations will be presented to ACTIV's Leadership Team and Executive Committee, which will collectively consider how prioritized projects should be distributed—through ACTIV, NIH, public-private partnerships, and/or industry alone.

To make the case for recommended activities, WG members will form subgroups responsible for developing a preliminary prospectus for each of five priorities they have identified. Dr. Menetski presented a list of those priorities along with volunteer and assigned group members; individuals can contact Dr. Menetski to request reassignment.



#	Strategic Objective	Description	Group Members
1	**Continue to harmonize and validate models, protocols and assays**	Continue our efforts to centralize up-to-date preclinical protocols and best practices to ensure robust data sets across sites and studies to standardize results and facilitate data comparison	• Jay Rappaport • Clint Florence • Isis Kanevsky
2	**Distill key findings to advance knowledge**	Consolidation, organization and dissemination of preclinical findings in a connected or centralized manner to keep the field up to date on major advancements in the field	• Prabha Fernandes • Isis Kanevsky • Tony Punturier
3	**Coordinate preclinical and clinical data and insights**	Enable better coordination between clinical study data and findings with animal model development and validation, particularly to address late stages of disease, comorbidities and long-haulers	• Thomas Cihlar • Josh Fessel • Clint Florence
4	**Develop a portfolio strategy for prioritization**	Focus on a strategic portfolio of agents that identify gaps in stages of therapy (e.g. oral antivirals to treat early infections, broad spectrum RNA antiviral for future pandemics, etc.) to address high unmet need areas	• Prabha Fernandes • Jay Grobler • Thomas Cihlar • Srinivas Rao
5	**Create a robust preparedness plan for the future**	Support preparedness for future pandemics by developing a playbook that consolidates lessons learned, assesses gaps in capabilities, and provides resources to target future pandemics	• Jay Rappaport • Josh Fessel • Kara Carter • Srinivas Rao

Discussion

Dr. Young emphasized that scenario planning must envision a resource structure sufficient to support a sustained pandemic response enterprise. For example, nearly all participants in ACTIV—from its own WG members to its most important collaborators, such as NCATS—have thus far donated their time while holding other full-time positions. A more sustainable staff structure is as important as funding in propelling their exemplary work into the future. One way to achieve this sustainability may be to pursue a continued public-private partnership. Industry groups have begun to explore what they might do to prepare for future pandemics, and many of their ideas overlap with ongoing discussions in ACTIV. Connecting these conversations may thus help create a fully resourced model that realizes long-term ambitions without duplicating efforts. Dr. Young promised to serve as a bridge between these efforts. Dr. Cat Lutz noted that resource identification also should address animal models that must be accessible immediately when a pandemic emerges.

As these conversations unfold, Dr. Christine Colvis stressed the need to think strategically about the ways that various partners can complement and harmonize with NIAID as the national leader in responding to emerging infectious diseases. The unique breadth of partnerships that ACTIV has already fostered—with NHBLI, NCATS, and NINDS as well as NIAID—put it in a strong position to continue mapping ways for participants to augment NIAID's work.

ACTIV's partnerships will also need to deepen internally. Dr. Young noted that Priorities (3) and (4) (preclinical/clinical data and portfolio strategy for prioritization) require the close collaboration of Preclinical and TX-Clinical WG members. He thus recommended that TX-Clinical WG members be invited to join the groups developing the vision for these priorities.

Dr. (b) (6) [redacted] suggested that these conversations may benefit from a review of parts of (b) (4) [redacted]

Subgroup Updates

In Vivo Strategy Subgroup

Dr. Nancy Haigwood is supporting the finalization of a draft of the NHP Field Guide effort that currently involves more than 80 people on 11 subcommittees. The group, which previously developed 42 highly detailed standard operating procedures, is working to create less exhaustive documentation (e.g., noting the existence of standard sample collection procedures rather than fully describing a necropsy).

Best Practices for COVID-19 Research in Small Animals Subteam

The last scheduled presentation to develop the Small Animal Model Field Guide was completed on October 7, 2020. This session exemplified the quality of the series, with a focus on hamster studies in BSL3 facilities that ranged broadly from collecting samples to animal husbandry to the potential implications of human lighting schedules on hamsters' nocturnal circadian rhythms and thus study outcomes. Videos of all presentations are available for viewing by WG members. An initial draft of the guide has been completed and reviewed, and the writer is revising content into a uniform set of bulleted step-by-step lists. Dr. Lutz will be available to assist with writing during an upcoming two-week period, as well.

Future Harmonization

The final Small Animal Model presentation revealed great potential for future harmonization efforts. Because the presentation was delivered by Dr. Adam Werts of Lovelace Biomedical (a CRO), other CRO representatives were invited and 46 attended. This broad attendance led to a poll of participants' interest in future sessions, which uncovered an unanticipated level of engagement. 100% of respondents said they would be likely to attend another session on similar topics; 80% expressed a willingness to participate in protocol harmonization with other CROs, academic BSL sites, etc.; and 40% indicated they were likely to make changes to their current work based on what they learned during the session.

WG members discussed the possibility of developing additional presentations in response to this interest. New topics will certainly become relevant as knowledge of COVID-19 evolves, creating space for a new topically-oriented presentation series. Possible topics might include mouse models of COVID-19 (focusing on a first wave of experimental data and/or on new genetically engineered models); best practices for CROs; or the human genetics influencing COVID-19 and the viral genetics of SARS-CoV-2 (e.g., a recent paper explored disease severity in humans as a contribution of the locus on chromosome 3, while popular press articles have suggested that genetic epidemiology has been generally overlooked in the United States, despite clear interest by some drug makers). Dr. Young suggested that this kind of discussion could identify resource needs on the strategic objective exercise—for example, long-term science writer support could be useful for keeping guides up to date.

Data Portal Implementation Subgroup

The Preclinical WG's two *Cell Host & Microbe* papers have been uploaded to the NCATS OpenScience Data Portal. A social media toolkit is now available for the portal's animal model pages and will be circulated with accompanying images.

Preclinical Network Subgroup

Twelve of fourteen new agents have been reviewed during Wave 4 agent prioritization; several were prioritized for hamster model studies and one sparked considerable enthusiasm. Two additional compounds will be considered this Friday 10/16 to complete Wave 4. The WG is considering how to share compound-related information with WG members without violating expectations of confidentiality. For example, high-level overview paragraphs or MOA-focused descriptions may be created.

Next Steps for Scenario Planning

All subgroups will perform a common strategic planning objective exercise that will lay the foundation for eventual proposals. Building on pre-populated forms created by Mr. Harrison Hawk, they will define the outputs that define success, the activities required to achieve those outputs, and the resources necessary to support those activities, as well as the factors that would change the strategic objective's urgency.

WG members agreed to hold a round of short meetings early during the week of October 19 to begin this exercise, with follow-up discussion during the next WG meeting if necessary. The WG will aim to present a set of five completed objectives to the Executive Committee at its next meeting in early November.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, (not in attendance) *Health Scientist, Project Officer, BARDA*

Ralph Baric, PhD, *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, (not in attendance) *Executive Vice President Infectious Disease, Evotec*

Marc Charette, PhD, *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, (not in attendance) *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, (not in attendance) *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, (not in attendance) *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Stephen Mason, PhD, (not in attendance) *Associate Research Fellow, Pfizer*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

Liz Ottinger, PhD, (not in attendance) *Project Manager, NCATS*

David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, (not in attendance) *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*
Sheri Hild, PhD, *Program Director for the National Primate Research Centers (NPRCs) at Office of Research Infrastructure Programs, NIH*
Isis Kanevsky, PhD, *Unit Director, Pfizer*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

FNIH STAFF

Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Manager, Monitor, Deloitte*
Sarah Connelly, PhD, *Senior Consultant, Deloitte*
Harrison Hawk, *Analyst, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li & Associates*

Appendix B: Chat Transcript

From cat lutz to Everyone: 10:12 AM
I will volunteer for distilling findings....

From Nancy Haigwood to Everyone: 10:15 AM
I would be happy to work on distilling and/or on preparedness for the future.

From Josh Fessel (NIH/NHLBI, he/him/his) to Everyone: 10:32 AM
Totally agree with Cat on the short meeting point. Status emailicus is a real phenomenon.

From William Florence to Everyone: 10:33 AM
Short meeting preferred. Email is bananas right now.

From Jay Rappaport to Everyone: 10:33 AM
Agree on the short meeting

From Prabha to Everyone: 10:36 AM
I like what Sarah suggested. get something in writing. think about consolidated thoughts and discuss for 30 minutes.

From Sheri Hild to Everyone: 10:41 AM
The 125 llbs of SOPs are with the NPRC Directors! They are pushing forward the Field Guide outlines.

From Prabha to Everyone: 10:48 AM
I really enjoyed Adam Werts's presentation because it was related to his experience—very personal view.

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed scenario planning for the WG's future. Members will each select from a list of strategic priorities those that they wish to develop further and will join small teams responsible for drafting a short prospectus for their selection.

Action Items

- Mr. Harrison Hawk will circulate slides compiling all scenario planning suggestions received by October 5 as well as the synthesis presented today.
- WG members will review the slides and then email Dr. Menetski and Mr. Hawk to indicate which priority they would like to develop into a prospectus. Based on responses, members will be grouped into small teams to draft those documents.

Scenario Planning Exercise

The Preclinical WG is scheduled to sunset at the end of 2020. Given the feedback from the WG, there are still gaps in the preclinical space that the ACTIV Preclinical WG is well-positioned to support through 2021. To determine whether such an extension is justified, the WG members have begun identifying preclinical research gaps and opportunities and discussing ways in which the WG could address those gaps if its remit were extended through December 2021. The WG collected and collated feedback from members to identify potential areas in which to focus continued work. Dr. Joseph Menetski presented a slide summarizing five potential priorities:

1. **Continue to harmonize and validate models, protocols, and assays:** Continue efforts to centralize up-to-date preclinical protocols and best practices to ensure robust data sets across sites and studies to standardize results and facilitate data comparison.
2. **Distill key findings to advance knowledge:** Consolidate, organize, and disseminate preclinical findings in a connected or centralized manner to keep the field up to date on major advancements in the field.
3. **Coordinate preclinical and clinical data and insights:** Enable better coordination between clinical study data and findings with animal model development and validation, particularly to address late stages of disease, comorbidities, and long-haulers.
4. **Develop a portfolio strategy for prioritization:** Focus on a strategic portfolio of agents that identifies gaps in stages of therapy (e.g., oral antivirals to treat early infections, broad spectrum RNA antiviral for future pandemics, etc.) to address high priority unmet need areas.
5. **Create a robust preparedness plan for the future:** Support preparedness for future pandemics by developing a playbook that consolidates lessons learned, assesses gaps in capabilities, and provides resources to target future pandemics.

Discussion

Some of the suggested priorities (e.g., Priority 2) might focus on synthesizing data generated by others. However, this group's expertise may be more effectively leveraged in updating recommendations around *novel* models and establishing their translatability—a goal that members considered one of the most important parts of preclinical research activities against a novel virus.

Priority 1: Harmonization and Validation

Although the Preclinical WG has done a great deal to harmonize and standardize preclinical research across sites and studies, more work remains. For example, last week's Small Animal Model Session was attended by numerous CRO representatives as these sessions just began to address the specific challenges that emerge in adopting best practices at an industrial scale.

Priorities 2 and 3: Key Findings and Preclinical/Clinical Data Coordination

WG members noted that Priorities (2) and (3) are intertwined: distilling preclinical findings would likely involve an effort to validate *in vitro* results based on ongoing clinical trials of drugs and biologics and thereby to develop a predictive preclinical model of what agents will be effective in humans at various disease stages. This work would require close collaboration between Preclinical and Clinical WG members. The effort would also likely have to grapple with the question of what standard of validation it would aim to meet.

Priority 4: Portfolio strategy for prioritization

The Preclinical WG (b) (5) [redacted] (b) (5) [redacted] Members identified several possible strategic priorities, including:

- (b) (5) [redacted]
- (b) (5) [redacted]
- (b) (5) [redacted]
  - Dr. (b) (4), (b) (6) [redacted] reported that NCATS has recently (b) (4) [redacted] (e.g., equipment and personnel) to (b) (4) [redacted]
- (b) (5) [redacted]

Prioritization depends on access to information about agents, but that information has not always been readily accessible during COVID-19. WG members suggested that a continued prioritization effort could seek to address this problem by facilitating more transparent and centralized data sharing.

Priority 5: Preparedness plan for the future

While the Preclinical WG's work has unfolded within the emergency of COVID-19, Dr. John Young noted that the integrated framework it has created could be proactively replicated for all viruses with pandemic potential so that a response infrastructure is available at any precise moment that it becomes necessary. Building on the WG's existing model, such a response infrastructure, could include the identification of animal models for similar viral strains, development of collaborative research networks, and a repository of accessible information. Participants laid out several elements of such an effort.

Ecosystem Approach

Building a proactive pandemic infrastructure would require the continued involvement of industry, which has expressed some interest in future pandemic preparedness. WG members suggested that NIH might be able to use its resources to forge a sustainable pandemic preparedness ecosystem—for example, by issuing new requests for proposals to help anticipate potential pandemic emergence. Such an effort could begin with a gap analysis to identify specific areas where research is needed.

Information Sharing

Any preparedness plan should address the need for information sharing. Many different groups responded to the COVID-19 pandemic, and many of them undertook similar activities. Information sharing is essential to ensure that efforts are not needlessly duplicated and that different data streams are gathered to support analysis on a larger scale.

Pandemic Surveillance

Pandemic surveillance may also be an element of pandemic preparedness, with monitoring to trigger new activities. Some work in this area is already done by NIAID and CDC. However, participants noted that this work did not detect SARS-CoV-2.

New Priority: Public Policy

Most of the proposed strategies take a "bottom-up" approach to pandemic response, beginning with studies to generate data. However, WG members agreed that a public policy framework can determine the availability of infrastructure to carry out such bottom-up approaches. For example, the existing infrastructure at NIAID enabled it to respond to COVID-19 in ways that other institutions could not. Further Preclinical WG efforts may examine public policy approaches and resources necessary to support pandemic response efforts.

Contingency Planning

Any future activities of the Preclinical WG will unfold in a continuously evolving landscape in which the most urgent needs may quickly change. Scenario planning should thus consider what contingencies would trigger alteration, escalation, or termination of efforts. WG members discussed several such possible contingencies and their implications.

(b) (5) [redacted]

WG members (b) (5) [redacted]. Members emphasized that they did not (b) (5) [redacted] although (b) (4) [redacted], some studies have shown (b) (5) [redacted] Members also expressed (b) (5) [redacted] Route of administration will also be important for early-stage treatment. For example, (b) (4) [redacted] in currently administered (b) (5) [redacted]

(b) (4) [redacted] also began last month). WG members noted (b) (5) [redacted]

Vaccine Approval
It will take time to confirm whether vaccines will completely protect from the disease (and for how long). (b) (5) [redacted]
However, (b) (5) [redacted], (b) (5) [redacted]. Members agreed that if COVID-19 (b) (5) [redacted] (b) (5) [redacted]. In addition, it is unclear how long any vaccine's protection will last; this risk is particularly concerning given the apparent possibility of reinfection. All of these factors argue for the need to continue drug development. Members also suggested, based on the experience (b) (5) [redacted]

Next Steps

Dr. Menetski displayed a template document that will allow WG members to create a preliminary prospectus for each of the identified scenarios of continued work. For each scenario, the template asks WG members to:

- Articulate a need in 2021 and beyond
- State the potential impact of addressing that need
- Identify the specific goals of work toward that need
- Outline the specific activities contemplated to achieve those goals, including resources required (e.g., time, funds, access to data, trials, or other tools) and expected outputs
- Define the factors that would mitigate or enhance the urgency of this need

These prospectus documents will make the case for leaders to invest in the activities identified by Preclinical WG members and create a framework for how to assign these activities across ACTIV, the NIH, and other initiatives.

Following this meeting, Mr. Harrison Hawk will circulate slides compiling all scenario planning suggestions received by October 5 as well as the synthesis presented today. WG members should review the slides and then email Dr. Menetski and Mr. Hawk to indicate which priority they would like to develop into a prospectus. Based on responses, members will be grouped into small teams to draft those documents.

Appendix A: Participants List

WORKING GROUP MEMBERS

Peter Adams, PhD, (not in attendance) *Health Scientist, Project Officer, BARDA*

Ralph Baric, PhD, (not in attendance) *Dept. of Epidemiology and Dept. of Microbiology and Immunology, UNC Chapel Hill*

Kara Carter, PhD, (not in attendance) *Executive Vice President Infectious Disease, Evotec*

Marc Charette, PhD, (not in attendance) *Division of Cardiovascular Diseases NIH, NHLBI*

Tomas Cihlar, PhD, *VP, and Head of Virology, Gilead*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Damon Deming, PhD, (not in attendance) *Virologist, Division of Antiviral Products, Office of New Drugs, FDA*

Michael Diamond, MD, PhD, (not in attendance) *Professor, Depts. of Medicine, Molecular Microbiology, Pathology & Immunology, Washington University*

Ken Duncan, PhD, (not in attendance) *Gates Foundation*

Prabhavathi Fernandes, PhD, *Retired, most recently led biotechs Cempra and DarPharma*

Josh Fessel, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Clint Florence, PhD, (not in attendance) *Program Officer, Research Resource Section, OBRR, DMID, NIAID*

Greg Gatto, PhD, (not in attendance) *Drug Development Regulatory Project Leader, RTI*

Jay Grobler, PhD, *Director, Infectious Disease Biology, Merck*

Nancy Haigwood, PhD, *Director and Professor, Oregon National Primate Research Center, OHSU*

Judith Hewitt, PhD, *Deputy Director, Office of Biodefense, Research Resources and Translational Research, NIAID*

Samantha Jonson, MPS, (not in attendance) *Special Assistant to the Director, NCATS*

Cat Lutz, PhD, *Senior Director, Mouse Repository & In Vivo Pharmacology, Rare and Orphan Disease Center, Jackson Laboratory*

Stephen Mason, PhD, *Associate Research Fellow, Pfizer*

Frank Nestle, MD, (not in attendance) *Global Head of Immunology Therapeutic Research Area and Chief Scientific Officer North America, Sanofi*

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David Payne, PhD, DSc, (not in attendance) *Vice President & Head, Medicine Opportunities Research Unit, GSK*

Louise Pitt, PhD, (not in attendance) *Director, Center for Aerobiological Sciences, USAMRIID*

Tony Punturieri, MD, PhD, *Division of Lung Diseases NIH, NHLBI*

Srinivas Rao, MBA, PhD, *Global Head Translational In Vivo Models, Sanofi*

Jay Rappaport, PhD, (not in attendance) *Director and Chief Academic Officer, Tulane Primate Center*

John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Isis Kanevsky, PhD, *Unit Director, Pfizer*

FNIH STAFF

Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Manager, Monitor, Deloitte*
Sarah Connelly, PhD, *Senior Consultant, Deloitte*
Harrison Hawk, *Analyst, Deloitte*

High-Level Meeting Summary

The Preclinical Working Group (WG) discussed scenario planning for the WG's future as well as updates from the *In Vivo* Strategy Subgroup and an upcoming staffing change.

Action Items:

- The excel sheet of the scenario planning exercise should be submitted to Mr. Hawk by Monday, October 5.
    - Per our discussion, we will prioritize the activities for 2021 (first sheet on the excel file). We will re-visit 2022 at a later time. (Additional context can be found in the "Scenario Planning Exercise" section of this document.
- Drs. Lutz, Kanevsky, and Menetski will edit the first version of the Small Animal Models Field Guide before submitting a working draft to the Subteam for review

Scenario Planning Exercise

The Preclinical WG is scheduled to sunset at the end of 2020, but it could potentially continue work during 2021. To determine whether such an extension is justified, the WG will consider preclinical research gaps and opportunities and discuss ways in which the WG could address those gaps if its remit were extended through December 2021. Suggestions should be entered into a pre-formatted template (already distributed to the WG in an excel format) and returned to **Mr. Harrison Hawk** (b) (6) [redacted] **by Monday, October 5** so that responses can be collated for discussion during the next WG meeting; WG members should note that although the template includes tabs for both 2021 and 2022 extension scenarios, suggestions for the 2021 extension scenario are the priority at this time.

When crafting suggestions for this extension, WG members should consider the following notes that were discussed during today's meeting:

- This will be the first iteration of this exercise.
- Suggestions do not need to be limited to the scope of the WG's current objectives.
- This is an exploratory exercise, not a commitment. Furthermore, suggesting an idea does not bind anyone to a leadership role in its execution.
- Suggestions may be expressed as bullet points and need not be in-depth. WG members should also feel free to leave sections of the submission template blank if they have no suggestions for that area.
- Focus on research gaps and opportunities that would have a high impact on the community.
- The outputs of the WG (e.g., agent prioritization, publications, preclinical resource networks, master protocols, field guides, data sharing infrastructure) may serve as a response framework for future pandemics beyond COVID-19.
- WG members should note when a suggestion would be directly impacted by the WG's potential decision to extend its activity through December 2022 (e.g., prioritization of compounds more than one year away from being clinic-ready).

- Several external factors may influence support for an extension of this WG, including results from vaccine and therapeutic trials, challenges with clinical trial enrollment, and increased focus on disease sequelae.

Subgroup Updates

In Vivo Strategy Subgroup

NHP Master Protocols and Field Guide: The NPRC Directors are scheduled to approve master protocols and SOPs this week. The Subgroup is also collating and planning the editing phase for the NHP field guide.

Viral Reference Strain Production: BEI will harvest a 1L production run of Washington strain viral stock grown on Calu-3 cells by October 15; preliminary data indicate that no single nucleotide polymorphisms (SNPs) are produced in up to three passages when the virus is propagated on Calu-3 cells. BEI is also performing parallel pilot production runs (50-100ml) in Vero E6/hSLAM, A549-ACE2, and Vero E6/TMPRSS2 cell lines.

BEI and NIAID have distributed aliquots of the HF1-NR-53870 stock (which contains one SNP not located within the furin cleavage site or Spike NTD); BIOQUAL was the first to compare this stock to a confirmed stock with furin cleavage site mutations in hamsters, and has started to return data that may indicate an effect of furin cleavage site mutations *in vivo*. Some genomic PCR data have also been received from an NHP study at Battelle. Updates on study progress will be provided to the WG when available.

Best Practices for COVID-19 Research in Small Animal Models Subteam

The Subteam has received the first version of the Small Animal Models Field Guide; Drs. Cat Lutz, Isis Kanevsky, and Joseph Menetski will work together on edits before providing a working version to the Subteam for review. The WG discussed the possibility of making some recorded presentations from Subteam meetings available online in addition to the Field Guide.

Staffing Update

In two weeks, Dr. Sarah Connelly will become the Preclinical WG's program management lead from Deloitte when Dr. (b)(6) departs for maternity leave.

Next Steps

The excel sheet of the scenario planning exercise should be submitted to Mr. Hawk by Monday, October 5. Per our discussion, we will prioritize the activities for 2021 (first sheet on the excel file). We will re-visit 2022 at a later time. Drs. Lutz, Kanevsky, and Menetski will edit the first version of the Small Animal Models Field Guide before submitting a working draft to the Subteam for review.

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John Young, PhD, *Global Head Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Ellen Gadbois, *Program Lead, Emerging Biotechnology Policy, NIH Office of Science Policy*
Isis Kanevsky, PhD, *Unit Director, Pfizer*
Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

FNIH STAFF

Joseph P. Menetski, PhD, *Associate VP, Research Partnerships, FNIH*

Rosa Maria Alvarez, PhD, *Manager, Monitor, Deloitte*
Sarah Connelly, PhD, *Senior Consultant, Deloitte*
Harrison Hawk, *Analyst, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From Josh Fessel (NIH/NHLBI) to Everyone at 10:06 AM

(b)(6), we will feel your absence greatly, but we are *delighted* that you'll be spending time with your little one(s?). Thank you so, so much for all that you've done!!!

From Prabha to Everyone at 10:07 AM

COngratulations (b)(6)! Thank you for your help and good luck.

From Prabha to Everyone at 10:08 AM

Prabha

From John Young to Everyone at 10:08 AM

Thank you Rosa for the great collaboration and support!

From (b)(6) to Everyone at 10:10 AM

Thank you all! When I joined I cut my maternity leave short to join this work - so now I'll go back to take care of my daughter. It's been a pleasure supporting this work and working with all of you :)

From Nancy Haigwood to Everyone at 10:58 AM

I must leave for another meeting. This plan of continuing field guides is great and we are attempting to make the NHP guide as general as possible.

ACTIV, Therapeutics-Clinical Master Prioritization Sub-Group

Working Group Meeting 1, Key Takeaways

Wednesday, April 15th, 2020

Action Items

Action Items		
	Information	**POC**
1	Subgroup review the full protocols of the top candidates for potential collaboration or structure use	**All Subgroup Members**
2	Draft options for proceeding quickly – New Trial vs. Existing Trials – for review on call tomorrow	**Stacey Adam/ Elizabeth Kim**
3	Poll for meeting of subgroup tomorrow 11am	**Stacey Adam/ Elizabeth Kim**
4	Share ACTG trial Master Protocol	**Judy Currier**

Key Takeaways

- **If faster than developing unique Master Protocol, reuse/enhance existing Master Protocol(s). If sub-group does develop unique Master Protocol, extract pieces from existing Master Protocols to make sure pieces are harmonized.**
- **Target patient populations: outpatient/moderate ambulatory, hospitalized but not in ICU, ICU patients (still under discussion)**
- **In terms of sequencing, focus on: (1) Hospitalized, non-ICU, (2) Moderate (Sick, but Ambulatory), (3) ICU (if pursued)**
    - **Move forward with master protocol development in waves (as is the approach of the Agent Prioritization group), in parallel processes (repurposed, clinically ready, pre-clinical, novel)**

Existing Master Protocols Overview

- ACTT, ACCORD, PRINCIPLE, RECOVERY, SOLIDARITY (WHO), REMAP-CAP, PREVAIL II presented as highly desired models
    - Actual protocols still needed for ACCORD and PREVAIL II for comparison
- Considerations from Sub-Group Chair:
    - WG needs to decide what Master Protocol features are important – some are early single detection protocols, some are trying to provide confirmatory evidence
    - Statistically: More frequent looks are reasonably well-accepted; need to be careful about sharing of controls when sharing across time.
    - Outcomes are critical.
    - Need to decide what we're trying to achieve and build a Master Protocol around that.
    - There is not real FDA guidance on Master Protocols that govern them all.
- Updates to group on Clinical Trial Network (CTN) working group (WG) meeting
    - CTN will focus on creating an inventory of clinical trial capacity that exists.. They will send a survey to the sites to assess capabilities and target patient populations.
    - Importance of fit-for-purpose approach in designing our trials.

  - CTN asks our Master Protocol Subgroup to identify patient populations to target. They asked MP Subgroup to assess:
    - **Prophylactic**
    - **Outpatient ill**
    - **Hospitalized but not in ICU**
    - **ICU patient**

(b) (4), (b) (6) [redacted] Presentation and Discussion

- Heads of R&D for most of major pharma in US have met for a few weeks. They are working on a similar effort to our TX-Clinical WG. (b) (4) [redacted]
- COVID R&D is focused on late stage compounds, with very large drug supplies, where a trial can quickly be started with what's available, and proofs of concepts with thousands/tens of thousands of patients can be launched in a few months.
  - (b) (4) [redacted]
- (b) (4) [redacted]
  - (b) (4) [redacted]
    - (b) (4) [redacted]
  - Data should be easily compared to/combined with other protocols and have credibility in regulatory settings.
  - (b) (4) [redacted]

Wednesday, April 15th, 2020

Additional Discussion Points

- If faster than developing unique Master Protocol, reuse/enhance existing Master Protocol(s). If sub-group does develop unique Master Protocol, extract pieces from existing Master Protocols to make sure pieces are harmonized.
- In terms of sequencing, focus on: (1) Hospitalized, non-ICU, (2) Moderate (Sick, but Ambulatory), (3) ICU (if pursued)
    - Move forward with master protocol development in waves (as is the approach of the Agent Prioritization group), in parallel processes (repurposed, clinically ready, pre-clinical, novel)
- ACTG has a trial for outpatient population that will come out May 1. Includes 33 sites, 2,000 patients, and is designed to add additional arms. It is a light touch outpatient study.
- ACTT has a good platform for repurposed agents and has just added it's second compound in addition to remdisivir, a JAK inhibitor. The trial has the capability to add more arms.
- ORCHID is using the PEDAL Network through NHLBI and is also looking at Hospitalized/Moderately Sick (Ambulatory) patients.

Wednesday, April 15th, 2020

Chatbox

From (b)(6) [redacted] to Everyone: 01:56 PM

I have a question about how we decide (b)(5) [redacted]

From (b)(6) [redacted] to Everyone: 02:00 PM

hey (b)(6) [redacted] : the key word (b)(5) [redacted]

From (b)(6) [redacted] to Everyone: 02:04 PM

I understand that the intent is not necessarily to have a (b)(5) [redacted]. That has a number of disadvantages, especially in infectious diseases.

From (b)(6) [redacted] to Everyone: 02:06 PM

No argument here, but I do like (b)(5) [redacted]

From elliottl to Everyone: 02:14 PM

worth clarifying FDA requirements...certain types of protocols may be incapable of satisfying them

From Stacey Adam to Everyone: 02:14 PM

Thanks Elliott, would you like to do that on the call or offline between our calls for reference?

From elliottl to Everyone: 02:15 PM

can be done offline

From Stacey Adam to Everyone: 02:16 PM

Okay, thanks

From (b)(6) [redacted] to Everyone: 02:27 PM

(b)(5) [redacted]? If so, what is the proportion?

From Stacey Adam to Everyone: 02:28 PM

Not sure Mark, but we can get that answer offline if not here

High-Level Meeting Summary

The Agent Prioritization Subgroup of the TX-Clinical Working Group (WG) decided to prioritize compounds in two primary categories: (1) *antivirals* and (2) *immunotherapies*. For both categories, the joint Steering Committee (SC), to be established by the WG, will first prioritize FDA-approved agents (i.e., for repurposing) and agents that are Investigational New Drug (IND)-enabled. Agents at the Phase I stage of development or earlier should be considered in future prioritization waves because they are not immediately eligible for clinical use. Aside from antivirals and immunotherapies, symptomatic or supportive therapies may also be considered (e.g., anticoagulants). The WG must first determine which agents are already being studied for potential applicability to COVID-19 and assess the robustness of those efforts.

In addition to therapeutic category, prioritization decisions must weigh the *patient population* and *stage of disease* targeted by a candidate therapeutic. These considerations are vital to ensure that agents are appropriately matched to a clinical context of use; populations most in need of effective therapeutics (e.g., those with severe disease) are aided as soon as possible; and clinical trial networks have access to the patient populations needed to test a specific asset, and in the numbers required to generate high-quality data to facilitate regulatory approval.

Crucially, no one set of agent prioritization criteria will be universally helpful; for example, safety data will not help differentiate among already-approved candidate compounds. Sets of criteria should be applied to specific *categories* of agents depending on their stage of development and target patient population.

Data Sources for Compounds

Existing Inventories

Various organizations are already assembling inventories of candidate therapeutic compounds for COVID-19, including (b)(4), the World Health Organization (WHO), the National Center for Advancing Translational Sciences (NCATS), and the (b)(4) as well as a group in the UK. FNIH has access to these databases (UK database forthcoming) to assist in the SC's prioritization efforts.

Post-meeting, Dr. (b)(6) suggested (b)(5) (b Combining information from such registries into a single dashboard that also provides information on the size and design of each trial would aid prioritization efforts. Dr. (b)(6) then clarified that several of the (b)(5) (e.g., (b)(4)) (b)(5)

Additional Data

For already-approved agents, regulators can provide detailed information from previous clinical and preclinical development and testing, such as PD, PK, MOA, toxicity, and target engagement. For any agents in earlier stages of development, ACTIV could issue a solicitation for companies to provide detailed information on compounds in their pipelines. Such a request for information (RFI) should solicit specific data that closely corresponds to the evaluation criteria used by the SC to prioritize compounds. Participants suggested focusing any RFI efforts on the second and subsequent waves of agent prioritization because such efforts will take more time than is available for completing the first wave.

Where relevant data are available, it will be important to consider the level of validation of an agent's target, as well as the agent's regulatory status (although the latter applies only to non-repurposed agents, which are lower priority than already-approved agents).

Agent Prioritization Process

Subgroup members agreed that agent prioritization should occur in two stages: First, a pool of subject matter experts (SMEs) should evaluate assets according to medical expertise (e.g., cardiology, virology, immunology, or coagulopathy). Second, compounds that the SMEs advance for further consideration will be received by the SC, which will be composed of three to four credible high-level experts who will decide final prioritizations among the SME-recommended agents.

Process Logistics

Participants suggested combining all information from existing agent inventories and prioritization efforts (e.g., lists of compounds with links to available data associated with each one) into a large spreadsheet and adding a column for SMEs to preliminarily evaluate each one. SME evaluations should then start by eliminating compounds that are already being adequately tested, unlikely to have therapeutic effects on COVID-19, or too early in development.

Thereafter, the SC should rank remaining agents according to questions such as the following:

- Which agents might address the highest-priority patient populations/stages of disease?
- Which agents are supported by the most robust and scientifically compelling test data?
- Which agents target mechanisms of action (MOAs) with the most compelling scientific rationales for relevance to COVID-19? Have other agents with those MOAs been tested?
- What is the feasibility of administering the agents to the target patient populations?
- Which agents could feasibly be manufactured and distributed at the scale required?
- Which agents exist in large enough quantities to adequately test in clinical trials?
- Which agents are in short supply for a vital patient population unrelated to COVID-19?

Additional Considerations

Even for approved agents, ACTIV may need to conduct phase 1 pilots to test whether the currently approved dose is appropriate for the target COVID-19 patient population. Participants suggested potentially developing a formal scoring system to ensure consistent application of all prioritization criteria. However, given the complexity of evaluating different categories of assets with different levels of available data, at varying stages of development, and for distinct patient populations, creating such a scoring system is not feasible, especially in the short time available.

Next Steps

FNIH will continue escalating requests for the UK inventory of candidate agents with potential relevance to COVID-19 and will circulate that list, along with the BARDA inventory, to Subgroup members when available. The Deloitte Technical Team will begin assembling a spreadsheet that integrates information from the various candidate agent inventories, and the WG co-chairs, Drs. Sarah Read and Eric Hughes, will begin developing a strategy and design for an RFI to solicit agents for the second wave of SC candidate reviews. Dr. Adam will also circulate a scheduling poll to identify feasible times for future Subgroup meetings.

Appendix A: Participants List

SUBGROUP MEMBERS

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Mike Poole, MD, *Venture Partner, Biomatics Capital; Therapeutic Accelerator Lead, Gates Foundation*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

Mike Vincent, MD, PhD, *Senior VP, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Rosa Alvarez, PhD, *Monitor, Deloitte*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

From (b) (6) **to Everyone: 05:34 PM**

Thank you for the new materials. Helpful.

From (b) (6) **to Everyone: 05:34 PM**

Very good. Glad they are.

From (b) (6) **to Everyone: 05:38 PM**

(b) (4) For example, (b) (4)

From (b) (6) **to Everyone: 05:39 PM**

There was some discussion that (b) (4)

From (b) (6) **to Everyone: 05:45 PM**

Sure, but these are hardly (b) (4)

(b) (4) Example (b) (4)

Yes, excellent approach

From (b) (6) **to Everyone: 05:50 PM**

(b) (4)

From (b) (6) **to Everyone: 05:54 PM**

Tim would you like to chime in on this third category?

From (b) (6) **to Everyone: 05:55 PM**

(b) (4)

From (b) (6) **to Everyone: 06:18 PM**

(b) (4)

From (b) (6) **to Everyone: 06:28 PM**

The (b) (4) studies are of course in progress.

High-Level Meeting Summary

The Therapeutics-Clinical (TX-Clinical) Working Group (WG) heard a presentation on the ACTIV-2 "Rise Above COVID" Campaign, provided feedback on the new NIH/ACTIV COVID-19 clinical trial matrix, and received updates on development and execution of each of its five master protocols.

ACTIV-2 Public Relations Campaign

The ACTIV-2 team has worked with Klick, a public relations firm, to create the Rise Above COVID Campaign, which seeks to engage affected and at-risk communities in the ACTIV-2 trial opportunity. Dr. Davey Smith presented to the TX-Clinical WG on this campaign, showing campaign graphics and other outreach materials in use. The Rise Above COVID Campaign uses search, branding, and marketing, as well as a website, contact center, and site hand-off mechanism, to promote ACTIV-2 enrollment. While branding and marketing are run by Klick, the Rise Above COVID Campaign also partners with the NIAID AIDS Clinical Trials Group (ACTG) for its COVID-19 Community Advisory Board, the CRO PPD for its healthcare provider contacts and patient enrollment infrastructure (e.g., to counter earlier messaging that individuals who had tested positive should stay home), and Jumo Health for its website design and execution capabilities. Rise Above COVID's website is accessible on every major device type (desktop, tablet, and mobile). The campaign also partners with various Black, Hispanic, and Native American community organizations to maximize enrollment of minority groups into ACTIV-2.

Next steps for the Rise Above COVID Campaign are to launch a social media campaign, initiate a collaboration with Google's Verily, issue advertisements at major big box testing venues, record a video to augment patient consent and recruitment, extend the campaign to assist other trials, and harmonize Community Advisory Boards across all ACTIV and Operation Warp Speed trials.

Discussion

Public opinion surveys could gauge people's attitudes to treatment and vaccine trials and thus help optimize public relations efforts. However, the ACTIV-2 and Rise Above COVID Campaign teams (b)(5) [redacted]

Dr. Judith Currier confirmed that all Rise Above COVID Campaign materials have been reviewed and approved by ACTIV-2's central Institutional Review Board. Dr. Currier will also distribute to TX-Clinical WG members a Zoom user background with Rise Above COVID Campaign messaging.

NIH and ACTIV Trials Matrix

Before this meeting, participants received a table with one axis describing patient populations and another describing various types of prophylactic and therapeutics interventions. The initial purpose of the table is to enable NIH and ACTIV leadership to identify potential gaps in the coverage of clinical trial efforts, with the intention to share a version that is restricted to publicly available information. Each cell lists clinical trials that are (1) NIH-sponsored/planned trials, (2) ACTIV trials, or (3) ACTIV-associated trials.

Discussion

To make the matrix more "user-friendly," participants stressed the need for detailed trial information to be available through clickable links in each box, and Dr. Sarah Read suggested enlarging the icons so that the matrix is easier to read. Note that the PDF version circulated to the group did not have the full mouse-over functionality of the PowerPoint version shown in the meeting.

Participants also suggested several adjustments to the content of the matrix. Dr. Currier noted that the matrix should be revised to show that ACTIV-2 enrolls symptomatic patients only. Drs. Lisa LaVange and Samuel Bozzette suggested changing the name of the "combination therapies" rows because the current name implies multiple experimental agents are provided in combinations, rather than the apparent intent of the row indicate that multiple different therapeutic classes (which are listed in parentheses) are included. Other participants suggested included both completed trials and ongoing trials, acknowledging that at some point there may be too many trials to fit in one table.

One change may make the matrix more effective when it is eventually made public: Dr. Jacqueline Kirchner proposed modifying the color scheme to match materials from the Rise Above COVID Campaign.

Master Protocol Subgroup Updates

The MPSG reviewed progress on its various master protocols (ACTIV-1/-2/-3/-4/-5).

ACTIV-1: Immunomodulators (Inpatient Phase III)

The ACTIV-1 team has finalized its master protocol based on the second round of Pre-IND feedback from FDA and plans to submit its IND application by September 14. The team also submitted its master protocol and Informed Consent Form to the Western IRB on September 8 and has reached full alignment with its DSMB. The team continues to work with NCATS' Trial Innovation Network (TIN), which will oversee all ACTIV-1 operational planning/implementation. The team has successfully selected 30 Clinical and Translational Science Awards (CTSA) sites (an additional site declined to participate) and has begun to evaluate non-CTSA sites in anticipation of selecting 17 additional sites for the trial; it has also begun to identify sites in four Latin American countries (Peru, Argentina, and Brazil, with Columbia as a back-up). BARDA has finalized contracts with TRI (the selected CRO), with DCRI and Syneos managing the U.S. and non-U.S. sites, respectively. The trial is expected to launch in late September or early October; next steps include finalizing paperwork with the selected CTSA sites, four of which already have Confidential Disclosure Agreements (CDAs) in place.

ACTIV-2: Monoclonal Antibodies (Outpatient, Seamless Phase II/III)

The ACTIV-2 master protocol launched on August 3 and as of September 10 has enrolled 10 patients and activated 18 sites (Dr. Currier noted that the first non-U.S. sites could be ready to begin patient enrollment by the end of September). The ACTIV-2 team is working with NIH and OWS leadership to assess and address study sites' resourcing needs to help support study enrollment/operations. The team continues to work with representatives from AstraZeneca to incorporate their agents into the master protocol and has initiated similar conversations with RU-BMS and Brii Bio. Next steps are to activate additional sites, conduct the trial, and report regularly on the trial's status to ACTIV and OWS leadership. Discussions are underway to establish clearer goals for minority recruitment into the trial.

ACTIV-3: Monoclonal Antibodies (Inpatient, Seamless Phase II/III)

The ACTIV-3 master protocol launched on August 4, and as of September 9 has (b) (4) and activated 19 sites, including its first non-U.S. site (in Denmark). The 20-patient DSMB Safety Review for (b) (4) nAb occurred on August 31, resulting in no safety concern. Thus, the DSMB encouraged acceleration of site opening and patient recruitment; a second DSMB review is planned for September 21. The team continues to work with representatives of (b) (4) to incorporate their agents into its master protocol, and it has initiated similar conversations with (b) (4). Next steps are to open additional sites, conduct the trial, and report regularly on the trial's status to ACTIV and OWS leadership.

Discussion

ACTIV-3's main task of activating additional sites has been somewhat hampered by the lack of a global regulatory framework to obtain IRB approval for all sites in a trial, and Dr. Libby Higgs suggested that creation of such a framework would assist international trials. Dr. Peter Stein confirmed that FDA is working to better coordinate its reviews of international clinical trial protocols to help ensure that regulatory agencies from various regions (e.g., FDA and EMA) can review identical protocols simultaneously to avoid delays.

ACTIV-4: Anticoagulants (Pre-hospitalized/Hospitalized/Post-hospitalized, Phase III)

ACTIV-4's pre-hospitalized protocol is expected to enroll its first patient by September 14, and its hospitalized protocol enrolled its first patient on September 4. Its post-hospitalized protocol has been finalized; drug has been supplied for this trial, which is expected to launch by the end of September.

ACTIV-5: Big Effect Trial (Inpatient, Phase II)

The ACTIV-5 team has finalized its master protocol, which was submitted on August 31 for IRB review and on September 2 to the FDA. A DSMB organizational meeting occurred on September 1, and site trainings for ACTIV-5's first four sites occurred on September 9. The trial is expected to launch the week of September 20, and the team is developing its agent prioritization process (which will include input from the TX-Clinical WG's Agent Prioritization Subgroup). Next steps are to address IRB and FDA feedback and continue to establish trial operations logistics and infrastructure.

Discussion

Dr. John Beigel noted that as of September 10, ACTT3 had (b) (4).

Appendix A: Participants List

WORKING GROUP MEMBERS

Neil Aggarwal, MD, *Lung Biology and Disease Branch Chief, National Heart, Lung, and Blood Institute (NHLBI)*

John Beigel, MD, *Associate Director for Clinical Research, Division of Microbiology & Infectious Diseases, NIAID*

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Judith Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, National Institute of Allergy and Infectious Diseases (NIAID)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (WG Co-chair)*

Andrei Kindzelski, MD, PhD, *Program Director, Division of Blood Diseases and Resources, NHLBI*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (WG Co-chair)*

Yves Rosenberg, MD, MPH, *Atherothrombosis and Coronary Artery Disease Branch Chief, NHLBI*

Daniel Rubin, PhD, *Division of Biometrics IV, CDER, FDA*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Michelle Culp, MPH, *Office of the Director, NIH*

Mary Groesch, PhD, *NHLBI*

Jacqueline Kirchner, PhD, *Senior Program Officer, Bill and Melinda Gates Foundation*

Robert Malone, MD, *Chief Medical Officer, Alchem Laboratories Corporation*

Hilary D. Marston, MD, MPH, *Medical Officer/Policy Advisor, NIAID, NIH*

Martha Petrovick, *MIT Lincoln Laboratory*

Lora Reineck, MD, *Program Director, Lung Biology and Disease Branch, NHLBI*

David (Davey) Smith, MD, *Professor of Medicine, U. California, San Diego*

STAFF

Michael Santos, PhD, *Associate VP, Science, FNIH*

Evan Appell, *Consultant, Deloitte*
Helen Q. Chen, PhD, *Manager, Deloitte*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

Sarah Read: 07:20

Hello everyone. (b)(6) is taking some very well deserved time off so Eric and I will be doing our best to fill in for her today!

Dave Hone – DTRA: 13:59

no, they reached out via the (b)(4) . very confusing data. passing them on to dr mac

Eric Hughes (EU): 15:05

what media will you use and how broadly?

Dave Hone – DTRA: 16:05

West world-esque hard to separate real from manufactured

Timothy G. Buchman: 16:13

Elegant campaign...

Libby Higgs: 17:05

Really like their graphics!

Timothy G. Buchman: 17:27

How will social media be used as a force multiplier? Will you leverage those who have signed up as potential vaccine trial enrollees as an "amplifier"?

Timothy G. Buchman: 18:18

Can you use those who have already participated in trials as an "amplified"?

Timothy G. Buchman: 18:23

amplifier?

Robertmalone: 18:56

I infer that the central IRB is reviewing all of this?

Currier, Judith, M.D.: 19:26

Confirming that central IRB has reviewed all materials.

Ruxandra Draghia-Akli: 19:35

What are the results of existing surveys on public sentiment/confidence regarding COVID, and the likelihood that they would enroll in the studies/vaccinate if a vaccine is available? In other words, what is the baseline?

Libby Higgs: 20:03

Recruitment materials have to be IRB reviewed.

Timothy G. Buchman: 20:54

Ruxandra is asking a key question. We seem to be entering a period of declining trust in public (health) officials.

Libby Higgs: 21:59

Reminds me of the sentiment during Ebola. Part of it is the fear incited by the outbreak itself. Restriction of freedoms, anger, etc.

Timothy G. Buchman: 23:49

Indeed. Somehow the reminder that the successes of (b)(4) ; ... have been achieved through trial participation--"breakthroughs that already have happened".

Neil Aggarwal: 38:13

Agree with Lisa.

Timothy G. Buchman: 41:06

Who precisely is the audience for this matrix?

Neil Aggarwal: 42:09

Are completed trials included?

Ruxandra Draghia-Akli: 54:40

Just being reminded - do we have the results from ACTT-2?

Ruxandra Draghia-Akli: 01:03:53

The ultimate regulator in the EU is not EMA but the European Commission

Neil Aggarwal: 01:06:32

Any updates on ACTT-3?

yves rosenberg, NHLBI: 01:06:59

Can ACTIV-2 PR efforts can be extended to ACTiIV-4 and others outpatient trials?

High-Level Meeting Summary

The ACTIV Therapeutics-Clinical Working Group (WG) received updates from each of its two Subgroups—Agent Prioritization and Master Protocol—after the Subgroups met this week.

Agent Prioritization Subgroup Update

The Agent Prioritization Subgroup decided to prioritize compounds in three primary categories: (1) antivirals; (2) immunotherapies; and (3) symptomatic/supportive therapies (e.g., anticoagulants) may also be considered. The Agent Prioritization Committee (APC), to be established by the WG, will first prioritize FDA-approved agents (i.e., for repurposing) and agents that are Investigational New Drug (IND)-enabled. Agents at the Phase I stage of development or earlier should be considered in future prioritization waves because they are not immediately eligible for clinical use. In addition to therapeutic category, prioritization decisions must weigh the patient population and stage of disease targeted by a candidate therapeutic. Prioritization decisions should also consider the feasibility of administering an agent to the desired patient population (e.g., invasive routes of administration may be infeasible for ambulatory patients).

Subgroup members agreed that agent prioritization should occur in two stages: First, a pool of subject matter experts (SMEs) should evaluate assets according to medical expertise. Second, compounds that the SMEs advance for further consideration will be received by the APC, which will be composed of three to four credible high-level experts who will decide final prioritization among the SME-recommended agents.

First Wave of Prioritization

In prioritizing compounds, the WG must first determine which agents are already being studied for potential applicability to COVID-19 and assess the robustness of those efforts. To assist both with this evaluation and with prioritization of compounds generally, the WG is building a master tracker spreadsheet compiling information about existing COVID-19 candidate compounds and clinical trials for assessment; this spreadsheet will include links to any available data associated with a particular compound. This master tracker spreadsheet should be available by next week, along with a final list of compounds being assessed in the UK, at which time the WG will begin eliminating compounds already being adequately studied to enable more detailed prioritization of the remaining compounds on the list. Dr. (b) (6) will confirm (b) (5) . Dr. (b) (4), (b) (6) will connect the WG with Dr. (b) (4), (b) (6) from (b) (4) , who has already (b) (4) :. As trials continue and additional data are generated, the WG aims to continuously funnel updated information into its master tracker to help inform sequential prioritization waves.

Subsequent Waves of Prioritization

For any agents in earlier stages of development, the Agent Prioritization Subgroup plans to issue a solicitation for companies to provide detailed information on agents in their pipelines. Such a request for information (RFI) should solicit specific data that closely corresponds to the evaluation criteria used by the SC to prioritize compounds. RFI efforts will support the second and subsequent waves of agent prioritization because such efforts will take more time than is available for completing the first wave. The Subgroup will need to determine who is best placed to issue the RFI for ACTIV.

Data Needed

Although prioritization criteria will vary somewhat according to an agent's therapeutic category and stage of development, WG members generally agreed that the following data types would be needed to prioritize agents:

- Mechanism of action (MOA)
    - Avoid duplicate tests of same MOA without compelling scientific rationale
- Stage of development
- Preclinical data
- PK/PD
- Safety/Toxicity
- Target population
- Regimen and route of administration
- Manufacturability/Scalability of agent
- Unintended consequences/Shortages of drug for existing patient populations
- Drug-drug interactions
- Cost of goods and availability worldwide
- Novelty
    - Orthogonality of the approach; how it is differentiated
    - Combinability

For already-approved agents, regulators can provide detailed information from previous clinical and preclinical development and testing, such as PD, PK, MOA, toxicity, and target engagement. For any agents in earlier stages of development, the WG's envisioned RFI can solicit those data.

Master Protocol Subgroup Update

The Master Protocol Subgroup agreed to pursue an adaptive global protocol that encompasses both inpatients and outpatients with the ability to administer various treatments. The Subgroup is considering two options: (1) Merge with or sign onto an existing master protocol (e.g., ACTT; inpatient); (2) Develop a novel master protocol, extracting design elements as appropriate from existing master protocol efforts. In either case, the nimble adaptive trial design will include a standard of care arm and will change as appropriate with new evidence.

ACTIV clinical trials will prioritize the following patient populations: (1) hospitalized/moderately ill and critically ill/ventilated ICU; (2) outpatient/ambulatory ill; (3) unaffected (i.e., prophylaxis). The WG will proceed with master protocols for the highest-priority patient populations first but will also develop other protocols in parallel for subsequent waves of clinical trials, such as those targeting prophylaxis.

Discussion

Participants discussed whether to join the existing ACTT master protocol or develop a custom protocol, considering the potential efficiency tradeoffs. Dr. (b)(6) noted that (b)(5) Participants agreed to examine ACTT's protocol in detail to determine how much adjustment it may require for ACTIV clinical trials. This evaluation will help the WG to assess efficiency tradeoffs of joining an existing master protocol versus developing a novel one.

Additional Suggestions

WG members suggested (1) aligning prioritization schematics across the Preclinical and Clinical Therapeutics WGs; (2) assessing availability of placebos for candidate compounds during agent prioritization; (3) sharing data capture templates across all WGs before they are issued to ensure capture of all information needed for agent assessment; and (4) compiling results from meta-analyses of existing clinical trials to help incorporate rigor of studies into agent prioritization.

Next Steps

FNIH and the Deloitte Technical Team will circulate the master tracker spreadsheet for agent prioritization next week, along with the UK's list of candidate compounds and the process used to prioritize those compounds. Agent prioritization criteria are essentially finalized although they may require minor modifications. The Agent Prioritization Subgroup and any volunteer experts from the main WG will begin eliminating and preliminarily prioritizing agents by the end of next week, aiming to generate a final shortlist by the end of April.

Co-chairs of the main WG and of the Master Protocols Subgroup, along with Dr. Lisa LaVange, will create protocol "repurposing" and "de novo" development timelines and assess the ACTT protocol in detail before the next WG meeting to determine whether ACTIV should join ACTT or develop its own master protocol for adaptive clinical trials. Based on that decision, Master Protocol Subgroup members will outline the requirements for ACTIV's master protocol design by the end of next week and then liaise with the Clinical Trial Capacity WG to align needs with resources.

Appendix A: Participants List

WORKING GROUP MEMBERS

Sam Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

Timothy G. Buchman, MD, PhD, *Biomedical Advanced Research and Development Authority (BARDA)*

Joan Butterton, MD, *Associate VP, Clinical Research, Infectious Diseases, Merck & Co.*

Sylva Collins, PhD, *Director of the Office of Biostatistics, FDA*

Judy Currier, MD, *Professor of Medicine in the Division of Infectious Diseases, University of California, Los Angeles (UCLA)*

Angelo DeClaro, MD, *Division Director (Acting), Division of Hematologic Malignancies, Food and Drug Administration (FDA)*

Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*

Mark Eisner, MD, MPH, *Senior VP, Global Head of Immunology, Infectious Disease, and Ophthalmology Clinical Development, Genentech*

Keith Gottesdiener, MD, *Former President and Chief Executive Officer, Rhythm*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (Co-chair)*

Elliott Levy, MD, *Senior VP Global Development, Amgen; TransCelerate Board Member*

John Mellors, MD, *Professor of Medicine, Chief of Infectious Diseases Division, U. Pittsburgh*

Sandeep Menon, PhD, *Senior VP and Head of Early Clinical Development, Pfizer*

Naimish Patel, MD, *Global Development Head of Therapeutic Area, Immunology and Inflammation, Sanofi*

Amanda Peppercorn, MD, *Senior Medical Director, Infectious Disease, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (Co-chair)*

Peter Stein, MD, *Director of Office of New Drugs, CDER, FDA*

INVITED PARTICIPANTS

Christine Colvis, PhD, *Director, Drug Development Partnership Programs, NCATS*

Elizabeth Desrosiers, MS, PMP, *Executive Director, Clinical Sciences and Study Management, Merck*

John Young, PhD, *Global Head Infectious Diseases and Early Development, Roche*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Elizabeth Kim, MPP, *Senior Consultant, Deloitte Consulting*

Joseph P. Menetski, PhD, *Associate VP of Research Partnerships, FNIH*

Michael Santos, PhD, *Associate VP, Science, FNIH*
Brett Tolman, MA, *Strategy Manager, Deloitte*
Karen Tountas, PhD, *Scientific Program Manager, FNIH*
David Wholley, MPhil, *Senior VP of Research Partnerships, FNIH*

Lucas Smalldon, MA, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

(b) (6) 26:20
The suspension of the moderate ill (b) (4) trial in China may serve as a caution that milder illnesses may be harder to engage.

default user avatar

Timothy Buchman 26:40
The suspension was said to be a low enrollment problem.

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Stacey Adam 27:06
Thanks, Tim, saw your hand up. Will try to work you in.

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Timothy Buchman 27:19
That was applause, not a hand!

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Stacey Adam 28:18
:)

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Timothy Buchman 31:38
Thinking about master protocols in the ICU, the Covid-19 patients are not "all the same". For example, about 60% have some evidence of acute kidney injury and about 1/3-1/2 of those (20-30% total) require renal replacement therapy. There seems to be in the US predilection of men, African-Americans and obese to have AKI and further to require RRT.

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Timothy Buchman 34:26
More generally, while the pathogen is homogeneous, their hosts are not and the expression is not uniform or even continuous. There are phenotypes.

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Timothy Buchman 54:04
Thank YOU!!!

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Mike Poole 54:22
Thanks everyone...

High-Level Meeting Summary

The Master Protocol Subgroup of the TX-Clinical Working Group (WG) reviewed patient population decisions from its initial meeting and developed a plan to create an ACTIV master protocol for candidate COVID-19 therapeutics. Members determined that no existing model protocol delivers all components needed by ACTIV and that the Subgroup will thus need to modify and repurpose an existing protocol or develop a new protocol. Members agreed to draft timelines for developing both new and "repurposed" protocols for assessment at the next meeting. The group also discussed the potential of assembling a draft protocol to discuss with the existing ACTT team to see if incorporate was feasible. A summary of the discussion follows.

Review of Key Parameters

The Subgroup reviewed and affirmed key parameters from its initial meeting. Members agreed that the ACTIV master protocol will be an adaptive, global protocol administering to inpatient and outpatient participants, with the potential to test a large number of treatments simultaneously and over time. An adaptive trial, in which the standard of care arm can change with new evidence, was universally desired.

The Subgroup reaffirmed the need for a flexible protocol to address patient populations across the spectrum of illness, with an initial focus on hospitalized patients. The Subgroup previously agreed to focus on two broad study populations: (1) hospitalized inpatients and (2) moderately ill ambulatory outpatients (in that order of priority), with prophylaxis deferred at this time. Members of the FDA were supportive of the broad approach for patient populations, noting ambulatory and prophylaxis populations could be pulled in as part of the same, or a different, protocol in the future.

Based on these parameters, the Subgroup focused on two critical issues: (1) refining patient populations and (2) determining the optimal approach for building a master protocol.

Refining Patient Populations

Members noted that the Clinical Trial Capacity (CTC) WG has defined similar patient populations using different names and expressed a desire to converge on terminology as ACTIV moves forward.

Parsing the Inpatient Population

Members noted that hospitalized inpatients can be divided into severely ill ICU and moderately ill non-ICU populations. While a master protocol could consider these populations independently, members generally agreed that combining the inpatient populations would facilitate greater understanding of compound efficacy and accommodate rapid changes in status for inpatients. Key considerations for delineating the inpatient populations center around the testing of *repurposed* compounds. Certain compounds are indicated for use only with end-stage approaches, and still others may not be well-characterized enough to be introduced in early disease. In addition, modes of delivery for existing compounds are often already optimized and may not be suitable for all patient populations (e.g., oral administration for patients on ventilators or intravenous administration for outpatients).

Selection of Endpoints

While endpoints may differ between patient populations, the Subgroup agreed that the ACTIV protocol should rely on clinical endpoints to evaluate the efficacy of proposed agents since surrogate endpoints (e.g., virological) are not yet reliable.

Developing the Optimal Approach for a Master Protocol

The goal of the ACTIV master protocol is to find the most efficient approach to study as many compounds as quickly as possible. To achieve this goal, three considerations were emphasized: (1) creating a *platform* that allows treatments to enter and leave as they are ready; (2) including a *precision health* element to address patient sub-types that may not be eligible for all treatments; and (3) planning for *optimization* of the protocol over time, in particular allowing the standard of care to evolve with new evidence. In addition, members agreed that any protocol should discourage the use of response-adaptive randomization. Members discussed the relative advantages of two specific approaches to developing a master protocol: (1) using existing protocols and (2) creating a new master protocol.

Existing Master Protocols

Several U.S.-based and international model protocols, (b) (5) [redacted]. Some protocols (e.g., (b) (5) [redacted]. However, members generally agreed that while all existing protocols could provide a (b) (5) [redacted] (b) (5) [redacted]. Dr. (b) (6) [redacted] (b) (5) [redacted]. However, (b) (5) [redacted]

New Master Protocol

A new master protocol could be designed to be expansive, allowing for testing of both existing compounds and the anticipated influx of new therapeutics. The Subgroup highlighted concerns about study site cannibalization, noting that sites may be more willing to participate in an expansion study than to take on a new study. However, a new protocol could create a unified testing strategy that may be helpful for public messaging as well as efficient research. In addition, to be the definitive COVID-19 framework, ACTIV would need a global reach, which could require design choices better achieved in a new protocol. The Subgroup highlighted two additional considerations for a new protocol:

- **Input from CTC WG:** A new master protocol should consider optimal networks, whether the protocol can be deployed in more than one network, and what IRB challenges that may present.

- **Harmonization:** Efforts across different protocols could be harmonized by prioritization of compounds. A major contribution would be developing consensus around targets, mechanisms, and therapeutic agents to be tested.
- **Pathway to Therapeutic Progression:** The group felt it would be ideal if the master protocol was able to conduct both smaller and larger studies, allowing for fast triage of compound, optimizing for agents with significant response rates that could progress quickly into a larger registration intent study.

Hybrid Approach

Members discussed adopting a hybrid approach that could maximize the advantages of existing and new protocols. One hybrid approach could use a repurposed protocol to test existing compounds more quickly, while developing a new master protocol in parallel to address the anticipated influx of new compounds later in the year. Some members expressed concern that such an effort could duplicate work and create mixed messages. To address these challenges, a modified hybrid approach could treat the new master protocol as a “master screening platform” that unifies different pieces of the hybrid. A repurposed protocol might also introduce so much change that it effectively turns an existing protocol into a new ACTIV master protocol.

Next Steps

The WG co-chairs and Subgroup chair will begin to prepare action item lists and timelines for developing that draft as an entirely new protocol or as a repurposing of an existing protocol (e.g., developing an ACTT 3). The Subgroup will reconvene to consider the two timelines and make further decisions about a repurposed, new, or hybrid approach. The co-chairs will also discuss whether drafting a new version of an existing protocol would best allow for assessment of incorporating it into and exiting protocol.

Appendix A: Participants List

SUBGROUP MEMBERS

Samuel Bozzette, MD, PhD, *Chief Medical Officer, National Center for Advancing Translational Sciences (NCATS)*

Joan Butterton, MD, *Associate Vice President, Infectious Disease Clinical Research, Merck*

Sylva Collins, PhD, *Director of Office of Biostatistics, CDER, FDA*

Judith Currier, MD, *Vice Chair, AIDS Clinical Trials Group (ACTG), UCLA*

Angelo DeClaro, MD, *Director (Acting) of Office of Biotechnology Products, CDER, FDA*

Mark Eisner, MD, MPH, *Senior Vice President and Global Head of Immunology, Infectious Disease and Ophthalmology Clinical Development, Genentech*

Keith Gottesdiener, MD, *President/CEO, Rhythm Pharmaceuticals (former)*

Eric Hughes, MD, PhD, *Global Development Unit Head, Immunology, Hepatology & Dermatology and China Region Development Head, Novartis (TX-Clinical WG Co-chair)*

Lisa LaVange, PhD, *Associate Chair, Department of Biostatistics, UNC (TX-Clinical WG Master Protocol Subgroup Chair)*

Elliott Levy, MD, *Senior Vice President, Global Development, Amgen*

Sandeep Menon, PhD, *Senior Vice President and Head of Early Clinical Development, Pfizer*

Amanda Peppercorn, MD, *Senior Medical Director, GlaxoSmithKline (GSK)*

Michael Proschan, PhD, *Biostatistics Research Branch, NIAID, NIH*

Dionne Price, PhD, *Director, Division of Biometrics IV, CDER, FDA*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID, NIH (TX-Clinical WG Co-chair)*

Daniel Ruben, PhD, *Division of Biometrics IV, CDER, FDA*

Yuan-Li Shen, *Deputy Director (Acting), Division of Biometrics V, CDER, FDA*

Mike Vincent, MD, PhD, *Senior Vice President, Chief Scientific Officer of Inflammation and Immunology Research and Development, Pfizer*

INVITED PARTICIPANTS FROM CTC WG

James Dickens, *Program Manager, NCATS*

John Farley, MD, MPH, *Director of Office of Infectious Diseases, CDER, FDA*

Peter Wung, *Deputy Director, Manufacturing Technologies, Sanofi*

STAFF

Stacey Adam, PhD, *Scientific Program Manager for Cancer, Foundation for the NIH (FNIH)*

Kelly Beazley, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Transcript

00:16:16 From DECLAROR to Everyone:

FDA agrees with a broad approach for the patient population and would also support registration approach as part of the master protocol

00:17:01 From Stacey Adam to Everyone:

Thanks, Angelo!

00:17:27 From sam bozzette to Everyone:

Suggest revisiting prophylaxis after we get further down the road with treatment. especially with what seems to be the high prevalence of asymptomatic disease, preventing infection among the exposed could have a major public health impact

00:18:23 From Stacey Adam to Everyone:

Sam, I think that is the plan. But we can definitely clarify if you would like.

00:19:04 From sam bozzette to Everyone:

I was not clear on that - thanks

00:19:06 From sam bozzette to Everyone:

thanks

00:21:03 From Amanda Peppercorn to Everyone:

outpatients would require different endpoints and schedule of assessments; will this be possible under one master protocol?

00:22:21 From Peter Wung to Everyone:

Adaptive design needs to be carefully considered especially with respect to sample size especially given the speed at which the study may be recruiting

00:23:52 From Stacey Adam to Everyone:

Amanda, I think we will deal with your question on the next slide.

00:24:01 From Stacey Adam to Everyone:

Thanks, Peter.

00:41:51 From sam bozzette to Everyone:

Agree with Judy

00:43:36 From sam bozzette to Everyone:

Agree with Keith too

ACTIV, Therapeutics-Clinical Agent Prioritization Sub-Group

Working Group Meeting 1, Key Takeaways

Tuesday, April 14th, 2020

Action Items

Action Items		
	Information	**POC**
1	Send WG members the (b) (4) of compounds (once received)	**Stacey Adam**
2	Send WG members the (b) (4) (If approved for release)	**Timothy Buchman**
3	Assemble master excel spreadsheet of all the data from the (b) (4) , (b) (4) (when received), and (b) (4) (when approved) (b) (4)	**Deloitte Technical Team**
4	Send (b) (4) to WG members for scheduling next sub-group meeting	**Stacey Adam/ Elizabeth Kim**
5	Begin building a strategy and design of an RFI to solicit "second wave" agents	**Sarah Read/Eric Hughes**

Key Takeaways

- At a high-level, focus on what candidates have been assessed, and what has not been assessed? From there, assess different populations and indications.
- Prioritize phase 2 and consider phase 1 in the longer-term. Sweet spot for this PPP may be repurposed drugs that are IND-enabled/FDA-approved.
- Potential for solicitation/RFI

Data Sources

- Existing databases will not have all of the information on the emerging compounds.
- Databases are very broad and approved agents would be available through EMA/FDA reviews for the safety profile.
    - What is not available is why EMA/FDA consider therapeutics appropriate for COVID-19, and why they would repurpose that drug for COVID.
- Suggestion to remove drugs that are moving forward in large clinical trials.
- We could request information on drugs in earlier phase/proprietary compounds from sponsors. Acquisition and assessment of these will be challenging.
- Request for master excel spreadsheet of all the data from the (b) (4) (when approved) (b) (4)
    - FNIH shared that Deloitte already contracted to assemble
    - Spreadsheet should have links to relevant original data when possible

Proposed Evaluation Criteria

1. Clinical Development Stage – 4 Groups
    - Repurposed

Tuesday, April 14th, 2020

- Candidates for Clinical Studies
- Preclinical
- Early Discovery

2. Therapy Types
    - Anti-virals
    - Immunotherapies/Host-Targeting Therapies
        - Small molecules and mAbs
    - Symptomatic/Supportive Therapies (i.e. anti-coagulants, etc.)
3. Involvement in Existing Clinical Trials (Is the agent covered sufficiently with good trial or not?)
    - Only duplicate trials when need for power or recapitulation of findings is needed
4. Suitable Patient Population (Can it cover only one category or many?)
5. MOA
    - Scientific Relevance/Interest
    - Other agents in class being well tested
6. Feasibility of Administration to Desired Patient Population (Route of Delivery)
7. Availability/Scalability of the Agent (Short-Term/Long-Term for Agents in "Second Wave"

Compound assessment – Criteria (aka Data Needed to Assess Agents)

- General Information Needed:
    - MOA
    - Stage of development
    - Preclinical data
    - PK/PD
    - Safety/Toxicity
    - Target population
    - Regimen and route
    - Manufacturability/scalability
    - Unintended consequences/Shortages of drug for existing patient populations
    - Drug-drug interactions
    - Cost of goods and availability worldwide
    - Novelty
        - Orthogonality of the approach; how is it differentiated
        - Combinability

NOTE: Criteria will not all apply to the different categories. Criteria will vary in importance based on the stage of development (preclinical, clinical).

- Additional Data to Collect (When Possible)
    - Important to consider how validated is the target. Prior clinical experience, exposure, and data is important.
        - Pre-clinical data, clinical data, epidemiological data
    - Regulatory status is an important consideration, but the group is prioritizing repurposed agents.